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VOLUME III June 1955 NUMBER 6

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# AMERICAN GERIATRICS SOCIETY

*Official Journal*

OF THE

AMERICAN GERIATRICS SOCIETY
AMERICAN THERAPEUTIC SOCIETY
TEXAS GERIATRICS SOCIETY

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ANNUAL MEETING—Chicago, Illinois—MAY 3 and 4, 1956

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THE JOURNAL OF
The American Geriatrics Society
*Official Journal of the American Geriatrics Society*

VOLUME III *June, 1955* NUMBER 6

# PROBLEMS OF CHEMOTHERAPY IN THE OLDER AGE GROUP*

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The goal of all chemotherapy is the elimination of parasitic disease with a minimum of effect upon the tissues and physiologic processes of the host. Strictly speaking, therefore, chemotherapeutic agents have no pharmacologic action, since they do not act upon the host. Rather, they interfere with certain vital systems of micro-organisms within the host, who serves as the growth medium for the invading parasites. Since the microbes which cause infectious disease are very much the same for all age groups, the general principles of chemotherapy apply to patients of later maturity in the same manner as they do to patients at any other stage of life.

However, a number of special problems are created by the changing conditions of the aging host and the effect that his altered physiologic state may have upon the fate of the chemotherapeutic agent in the body and, more importantly, upon the significance of untoward reactions encountered with each particular drug.

In order to expose these special problems completely, it is first necessary to consider the two vital, etiologic factors involved, namely, A) the aging process, and B) the undesirable features of chemotherapeutic agents.

## A. Some aspects of the aging process which have a bearing upon infections

Among other progressive degenerative alterations, the aging process itself causes specific physiologic changes in structure of tissues, functional activity, homeostatic mechanisms and immunologic responses. It should be remembered, however, that much of the disability of those past the so-called prime of life is due to chronic progressive disease rather than to age alone.

Bickerman (1), discussing resistance to infections in the respiratory system

* Presented before the Graduate Symposium on Geriatric Medicine given by the American Geriatrics Society, New York, N. Y., November 12 and 13, 1954.

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in the aged, presents a lucid account of important changes. He points out that the old individual is less reactive to stimuli, as the finer central mechanism of adjustment is dulled, and the speed of response diminished. Lymphoid tissue, the macrophage system and the spleen undergo atrophy, thus diminishing the capacity for the production of antibodies. The bone marrow, slowly replaced by fat and connective tissue, loses its faculty to respond to infection. The processes of repair are impeded or may even cease to operate. There is atrophy of the glands of internal secretion, many of which are intimately concerned with the underlying mechanism of natural resistance. Deficiencies of absorption and excretion and nutritional deprivations lessen the organism's power to resist infection.

In general, then, the influence of old age consists in modifying the character, rather than initiating different forms of infectious disease. Thus diseases common to all, or most stages of life are in old age less acute and dramatic, and more prone to be latent. Indeed, there is often an amazing poverty of constitutional and local reactions to injury and infection (2, 3).

In many instances, therefore, the course of acute infections in older people does not follow the pattern observed in younger patients. It is well known that even a major form of acute respiratory disease, such as pneumonia, may be so completely masked due to lessened reactivity of the patient that it remains undetected during life. Even when discovered, treatment may be more difficult because of the dearth of typical signs and symptoms of the disease. On the other hand, older persons of a more robust constitution may respond to the infection like young adults and exhibit the characteristic picture of the particular disease.

**B. Undesirable features of chemotherapy, of particular importance in the aged**

In older people the functional power of all tissues is altered, among other factors, because of changes in the capillaries which set up degenerative changes of the intracellular medium. Consequently, the absorption, distribution and metabolism of drugs is often considerably slowed so that the response to drugs in general, and to chemotherapeutic agents in particular, may be altered. Delayed elimination, due in part to reduced renal function, may contribute to drug retention and greater concentration in the tissues than in the young individual. This suggests caution in the administration of drugs excreted primarily by the kidneys. Greater attention to dosage, blood levels, solubility and the nephrotoxic qualities of drugs is imperative in such instances.

Complications induced by antimicrobial agents have been discussed frequently in detail (4, 5, 6). However, the literature contains few special references to the geriatric aspects of this problem (7).

Untoward reactions and complications of chemotherapy which may assume special significance in patients of the older age group are represented within the following three categories:

1. Sensitization reactions
2. Nephrotoxic reactions
3. Complications due to microbial resistance.

1. *Sensitization reactions*

It has been reliably estimated that American drug houses have sold in 1953 alone, antibiotics in a total amount valued at 250 million dollars. If the sale value of other chemotherapeutic agents such as the sulfonamides and tuberculostatic adjuvants is included, the figure actually reached the 300 million dollar mark. This enormous use of antimicrobial agents on an aging population has resulted in rapidly increasing percentages of sensitization reactions, particularly for penicillin, the antibiotic employed longest, most widely and in the highest concentrations (4). It is of interest that the increasing incidence of allergic reactions observed with increasing dosage of penicillin is in good agreement with a concept that I presented in 1948 (8), namely, that within limits, the incidence of *production* of sensitization is directly proportional to the tissue concentration of the sensitizing agent.

Drug rash and fever are sensitization reactions which may occur with all chemotherapeutic agents. They are usually of little consequence if therapy with the particular agent is promptly discontinued. Serious complications such as exfoliative dermatitis or other severe reactions of hypersensitivity are, fortunately, rare.

It is believed by some that drug sensitization may occasionally induce periarteritis nodosa. Others feel that this lesion of unknown etiology should be distinguished from hypersensitivity angiitis (9). The sulfonamides were implicated first. More recently penicillin, streptomycin and possibly other antibiotics have been considered capable of eliciting the same type of vascular damage (5).

Very serious, and probably apt to occur more often in the older age group, are the anaphylactoid reactions seen especially with increasing frequency in association with penicillin therapy (10). They undoubtedly are related to the large amounts of penicillin which have been used in this country in the last ten years.

In 1953 the Food and Drug Administration made a survey to determine the number of acute anaphylactoid reactions attributable to penicillin and other antibiotics. This was a spot survey which encompassed the ten largest cities in the United States and uncovered a total of 84 anaphylactoid reactions, 24 of which were fatal. None of these had ever been reported in the literature. Only 4 reactions were uncovered as due to streptomycin (with 1 fatal outcome), and none due to broad-spectrum antibiotics.

On the basis of this survey, it was estimated that 100 to 200 anaphylactoid reactions from penicillin occur in this country in one year, and that about 30 per cent of these reactions are fatal (11).

Unfortunately, further substantial increases in the incidence of allergic reactions must be expected in an aging population that starts its first day of life with antibiotic eyedrops and antibiotic ointments, and receives a variety of antibiotics during childhood and adult life.

2. *Nephrotoxic reactions*

The high percentage of renal impairment due to arteriosclerotic cardiovascular-renal disease, or as the sequelae of systemic infections or ascending urinary

infections in older people, makes it imperative to avoid as far as feasible any undue burden or irritation that may be placed upon such kidneys by chemotherapy.

Before the introduction of the sulfonamide-mixture principle (12), the low solubility of highly active systemic sulfonamides, such as sulfadiazine or sulfamerazine, represented a serious disadvantage of these compounds because of the danger of crystalline obstruction of renal tubules. This danger is not always reliably offset by alkalization, which, moreover, is often contraindicated in patients with cardiovascular-renal conditions because of the excessive sodium load. Hence many authors felt that sulfonamide therapy in the elderly was hazardous.

However, the drawback of renal complications has been eliminated for all practical purposes through the use of the sulfonamide mixtures. By combining, for instance, partial dosages of several sulfapyrimidines, the unsurpassed therapeutic activity of these sulfonamides can be readily maintained or even enhanced (13, 14, 15), whereas the unsatisfactory solubility of the separate sulfadiazines is raised above the danger level, even in the more acid physiologic pH range of human urine (16, 17). Thus, the threat of renal complications is minimized, without the burden and dangers of alkalization and without loss in therapeutic efficacy. Sulfonamide triple mixtures can therefore be safely used for the treatment of systemic infections, even in advanced age, although impairment of renal excretory function or urinary retention may call for reduction of dosage and a closer check upon the blood level in order to avoid cumulation.

This latter precaution applies obviously also to the dosage of antibiotics. Penicillin is non-irritant to the kidneys. However, its retention in the body because of marked slowing of renal excretion is not without danger and may lead in rare instances to convulsions and even death when excessive dosages are employed (18).

The broad-spectrum antibiotics likewise do not seriously interfere with renal function, whereas streptomycin, and especially neomycin, bacitracin and polymyxin B may induce considerable tubular damage. The use of the latter agents should therefore be limited to dangerous infections in which other drugs are ineffective. Advanced renal impairment presents a strict contraindication to the systemic use of the three last named antibiotics.

### 3. *Complications due to bacterial resistance*

Selbie (19), in examining the problem of bacterial resistance to antimicrobial agents, came to the conclusion that, "the general practitioner can use the sulphonamides and penicillin for the infections for which they are indicated without fear of creating resistance in the infecting organisms or increasing the prevalence of resistant infections. On the other hand, one must use streptomycin and the later antibiotics with caution, keeping in mind that the infecting bacteria may acquire resistance during treatment."

Although therapy with the sulfonamides may not create resistance in the infecting organism, the outgrowth of resistant infections was undoubtedly observed in the early years of sulfonamide application. Yet, it remained for the

antibiotics to introduce the picture of new and often fulminating "super infections." Apparently these more powerful antimicrobial agents may so disturb bacterial balance and antagonism in the host as to aid substantially the outgrowth of micro-organisms not responsive to the particular antibiotic in use. Thus, new disease entities and new problems were introduced into therapy, which are of particular importance in geriatrics.

The organisms that have been observed to increase most frequently during antibiotic therapy are Proteus vulgaris, Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans (monilia) (5,20,21). These "super infections" are perhaps the most serious complication of the widespread use of antibiotic agents.

In patients with pulmonary disease, the new infection may occur as a superimposed bacterial pneumonia. In the urinary tract, infections often manifest a complete change of their bacteriologic character, and may even become more severe because of the elimination of bacterial antagonists. Similarly in the intestinal tract, eradication of sensitive bacteria encourages in particular the outgrowth of monilia or staphylococci. These organisms may become invasive and produce serious generalized infections. More often, however, their presence in the gut in massive concentration, possibly aided by the irritant qualities of orally administered antibiotics and the liberation of an enterotoxin, results in severe damage to the intestinal mucosa (pseudo membranous colitis) (22, 23), which is invariably associated with profuse watery diarrhea.

This entero-colitis or dysentery, which is of staphylococcal origin in the majority of cases, may result in deterioration of the patients' condition at a time when the primary infection (*e.g.*, pneumococcal pneumonia) was being eliminated. It thus may prolong the period of morbidity of many patients and may even play an important role in the failure of others to survive. The diarrhea, also known as the choleriformic syndrome, which may follow the oral administration of the tetracyclines, is explained by Poth (24) as possibly due to the following sequence of events. When the bacterial flora of the gut is markedly suppressed on the third to fourth day, proteus organisms grow out quite regularly and may cause diarrhea. Should a resistant staphylococcus develop, it produces a potent enterotoxin, and nausea, vomiting, bloody diarrhea, hyperpyrexia, collapse and death may result.

It is of interest that diarrhea may occur in as many as 20 per cent of hospitalized patients treated with a daily dosage of 1.5 Gm. of oxytetracycline (Terramycin) and that a substantial diminution of this complication can be accomplished by holding the twenty-four hour dosage to 1 Gm. (250 mg. every six hours). On an equal dosage basis, the tendency to produce staphylococcic diarrhea is apparently significantly lower for chlortetracycline (Aureomycin) (25).

Spink, discussing the problem of antibiotic-resistant staphylococci which may occur spontaneously or during antibiotic therapy (26,27), reported that the increase in cases of severe staphylococcus sepsis with septicemia at the University of Minnesota Hospitals during 1952 and 1953 was "disheartening." The overall mortality rate was over 50 per cent, and 90 per cent of the patients who died had acute bacterial endocarditis. The results of surgical procedures on

the prostate gland, and in the abdominal and thoracic cavities, were marred by fatal postoperative infections due to contamination of the wounds with resistant staphylococci. Some strains produce a dermonecrotoxin which may cause extensive ulcerating lesions of the skin, subcutaneous tissues, and even the muscles. Spink emphasizes that in attempting to treat staphylococcic sepsis with antibiotics selected on the basis of *in vitro* sensitivity tests, one must be as aggressive and as persistent as in the therapy of subacute bacterial endocarditis due to alpha hemolytic streptococci. Premature discontinuation may cause fatal relapses.

Although the grave danger of such complications, particularly in the elderly, cannot be minimized, it is imperative that it be seen in true perspective, so that no patient who really requires penicillin or broad-spectrum antibiotics be denied the benefits of such medication. It appears from a review of the literature that fortunately the incidence of staphylococci resistant to antibiotics has increased to a considerably less degree in the general population than might appear from studies in hospital patients (11).

*Treatment.* To combat these dangerous complications, the following points should be kept in mind: 1) Considerable care and discretion should be used in the selection of patients for treatment with the potent antibiotics—including penicillin, which is still the least toxic of those now available—because their administration may be followed by serious and even fatal reactions. The routine use of broad-spectrum antibiotics for minor or doubtful indications, as well as for prophylaxis, is definitely contraindicated. 2) When using any of the tetracyclines orally, the minimum effective therapeutic dose should be employed. This will decrease the likelihood of irritating the intestinal mucosa and of disturbing the normal antagonism among the flora of the intestinal tract, which may be the medium for prevention of the outgrowth of pathogens such as staphylococci. Chlortetracycline should be used in preference to oxytetracycline. Cathartics should be avoided during therapy with tetracyclines, since the added irritation may precipitate the onset of diarrhea (25). 3) If diarrhea occurs on or after the third day of antibiotic therapy, oral administration should be promptly discontinued, especially if staphylococcal etiology is suspected or established. Other antibiotics like erythromycin, carbomycin, bacitracin or chloramphenicol may be tried in the treatment of the staphylococcic infection. However, strains have begun to emerge with increasing frequency which are resistant to these antibiotics also. 4) Aseptic precautions, even to the point of isolating severely ill, debilitated patients under antibiotic therapy, may aid in minimizing the danger of cross infection from patient to patient, or from healthy carriers (hospital personnel). As a routine measure and for the same reason, streams of handshaking visitors should be reduced to the minimum necessary trickle at a proper distance from patients under therapy with powerful antibiotics, whether in the hospital or in the home.

## APPRAISAL OF CHEMOTHERAPY

From this discussion it will be clear why the over-enthusiasm that greeted the appearance of each new antibiotic has given way to sober evaluation of

their shortcomings, which must be accepted with their advantages. This has had two salutary effects:

1. Reduction in the number of patients who receive antibiotic therapy unnecessarily and who may suffer serious consequences from it.

2. Conspicuous resurgence of older and well-established therapeutic measures, such as treatment with the sulfonamides. This form of therapy actually was never abandoned by the practising physician, and in recent years has been further improved through the development of preparations of maximum efficacy and minimum toxicity.

## CHEMOTHERAPY IN THE AGED

In the face of the facts presented, the problems of chemotherapy in the older age group may now be brought into sharper focus.

The drugs used, as well as the mode of their application, are very much the same in old as in young individuals. This would apply in particular to typical serious infections occurring at any age, such as septicemia, peritonitis, meningococcal meningitis, or subacute endocarditis. However, in the aged we are facing the additional problems of less competent homeostatic mechanisms and organic alterations, due to degenerative changes and intercurrent and chronic disease, which may have an important bearing upon the dosage of chemotherapeutic agents and the significance of their toxic reactions. This calls for greater watchfulness with respect to chemotherapy in the older patient. Moreover, the dearth of signs and symptoms, even of major infections, in advanced senescence may not only delay discovery of the infection but interfere with the interpretation of chemotherapeutic efficiency.

Finally, one is faced in the chemotherapy of older patients with a greater prevalence of *chronic* infections, often of a mixed flora which would be more difficult to eradicate even in a vigorous, young individual. I am thinking in particular of bronchopulmonary and urinary infections. Advancing age calls for the more frequent use of major, and especially intestinal surgery and thus for the more frequent need of chemoprophylaxis. It is in these three areas of application, which are of particular importance in the older age group, that some additional considerations appear in order.

### *Chemotherapy of chronic broncho-pulmonary disease*

In a recent editorial of the Journal of the American Medical Association (28), a new therapeutic trend is illustrated, consisting in the continuous or intermittent long-term use of chemotherapy in chronic broncho-pulmonary disease. Penicillin in dosages of 250,000 units three times daily by mouth, and sulfadiazine in dosages of 1 gram to 3 grams daily, are considered the best forms of therapy, in that sequence.

It is obvious that patients with chronic or recurrent respiratory diseases such as chronic bronchitis, infectious asthma or bronchiectasis, will be prone to frequent acute recurrences which in turn will tend to perpetuate and make irreversible the underlying pathologic condition. Cases of this kind apparently respond well to long-term prophylactic sulfonamide or antibiotic therapy. Such long-term

therapy has for some time been considered indispensable for the prevention of acute streptococcal infections in persons susceptible to rheumatic fever. This new development extends the usefulness of prophylaxis to a large group of patients, including the elderly.

However, the therapeutic objective changes with the age group. In children and in young adults with pulmonary infections, for instance, the major objective is usually to keep the acute bronchial infection from developing into an irreversible pathologic state, whereas in older patients with an already established pulmonary condition, the primary aim is the prevention of acute infections or exacerbations of the chronic condition which may precipitate respiratory acidosis or acute anoxia (29).

It is well known that patients with chronic pulmonary disease are extremely susceptible to superimposed respiratory infections. Such infections may embarrass respiration sufficiently in the patient with bronchial asthma, bronchiectasis or pulmonary fibrosis, to result in cardiac failure or fatal anoxia; thus, they must be treated promptly. Since the diagnosis of intercurrent respiratory infection is often particularly difficult in older patients with pre-existing chronic respiratory disease, the suggestion seems appropriate that it is advisable to use prophylactic therapy to prevent such infections, rather than wait for the serious acute conditions to develop (30, 31).

For this type of prophylaxis or therapy, combinations of penicillin with a sulfadiazine triple mixture (32) appear to have particular advantages for the following reasons: 1) As has been pointed out, upper respiratory infections are generally associated with a mixed flora, including Str. hemolyticus, Str. viridans, Str. nonhemolyticus, Staph. aureus, Neisseria, diphtheroids and pneumococcus, all of which are sensitive to both penicillin and the sulfonamides. 2) In addition there may be gram-negative strains, unaffected by penicillin, the outgrowth of which is actually aided by the suppression of gram-positive bacteria. Thus the development of serious "super infections" may be prevented by the simultaneous presence of the sulfonamides. 3) Penicillin and the sulfonamides are often synergistic in action, as has been shown (32–38) in numerous experimental and clinical studies. 4) Sulfadiazine triple mixtures (sulfadiazine, sulfamerazine, sulfamethazine) afford excellent blood and tissue concentration while minimizing the danger of renal concretions (39). *In vitro* studies of 263 bacterial strains isolated from hospitalized patients (40) demonstrate that sulfonamide mixtures have greater antibacterial action than equal weights of single sulfonamides, and that adding penicillin to the mixture not only increases the potency, but the range. These findings have been confirmed in laboratory and clinical investigations (33, 40, 41).

*Urinary infections*

In spite of a battery of powerful antimicrobial agents, it must be admitted that the eradication of chronic urinary infection still presents a difficult problem in many instances. It has become abundantly clear that the presently available antibiotics are not the answer. In fact, the sulfonamides are effective against a greater variety of organisms than are most of the antibiotics. In cases of

simple acute cystitis sulfonamides are effective against most of the common causative organisms, with the exception of α-Streptococcus faecalis. Treatment may therefore be begun at once, with the probability of rapid cure in a considerable proportion of cases. In mild infections small dosages (0.5 gram, four times daily) may be adequate, and except for previous history of sensitization, untoward reactions are rarely encountered (8). Serious infections, especially those involving the kidney (pyelonephritis), require full therapeutic dosages.

In the elderly patient with usually impaired renal function, it is advisable to employ only sulfonamide preparations of reliable solubility, such as a sulfadiazine triple mixture (sulfadiazine, sulfamerazine, sulfamethazine) when higher blood and tissue concentrations are desired, or the single soluble sulfonamides, such as sulfacetamide (Sulamyd®), sulfisoxazole (Gantrisin®) and sulfamethylthiadiazole (Thiosulfil®) when the maintenance of high sulfonamide tissue levels appears of less importance—for example, in simple cystitis.

Although any one of the sulfonamides enumerated may be superior to the others in a particular instance against one particular strain, claims of a wider antibacterial spectrum or of special antibacterial specificity for some specific one among these agents have not been substantiated.

With regard to the antibiotics, penicillin is indicated only against certain gram-positive infections and is best used in combination with sulfonamides. Streptomycin, although highly active against gram-negative urinary pathogens *in vitro*, as a rule loses its value in clinical application within days, because of the rapid development of complete bacterial resistance. The tetracyclines, chloramphenicol, polymyxin B and neomycin, should be reserved for infections not responding to sulfonamide therapy, because of their potentially dangerous toxic reactions which, as has been outlined, may be more deleterious than the urinary infection itself.

*Chemoprophylaxis in surgery*

As at any other age, there is no serious objection to the routine use of intramuscular injection of penicillin-streptomycin combination before major surgical intervention, if the limitation of this precautionary measure is not lost sight of and no undue feeling of safety is created in the surgeon's mind by its application. Although the theoretical value of protection against both gram-positive and gram-negative organisms may appear attractive, it should be remembered that streptomycin often becomes ineffective against a large number of gram-negative bacteria within a matter of days. Hence, the surgeon must remain on the alert against invasion by streptomycin-resistant gram-negative bacteria, and institute prompt counter-measures with suitable agents, if grave complications are to be avoided. The sulfonamides and broad-spectrum antibiotics may be considered as the first line of defense in this situation. Only if the infection cannot be controlled by these agents, should the systemic use of neomycin, polymyxin B or bacitracin be considered. Moreover, it will be clear from what has been said earlier that the surgeon faces the serious problem of wound infection with staphylococci resistant to antibiotics.

Prophylaxis with suitable agents is definitely indicated when contaminated

parts of the body have to be entered, such as the bowel, the respiratory tract or the genito-urinary tract. It becomes imperative in the presence of valvular heart lesions, because of the danger of ensuing subacute bacterial endocarditis.

In preparation for bowel surgery, systemic broad-spectrum antibiotics should not be used as a rule, because of the danger of severe diarrhea and entero-colitis. According to Poth (24), best results in gut sterilization can be achieved by combining one of the poorly absorbable sulfonamides with neomycin, which is also not absorbed when administered orally. Poth seems to favor phthalyl sulfathiazole (Sulfathalidine®) somewhat over phthalyl sulfacetimide (Thalamyd®) or succinyl sulfathiazole (Sulfasuxidine®). The dosages of these drugs are: phthalyl sulfathiazole or phthalyl sulfacetimide, 4 grams daily; succinyl sulfathiazole, 12 grams daily. The dosage of neomycin is 6 grams daily. The combination of sulfonamide and neomycin can be given for two to three days prior to gut surgery.

Poth emphasizes that neomycin alone is not a reliable gastrointestinal antiseptic, because in 10 per cent of the cases it does not prevent the outgrowth of Aerobacter aerogenes. In addition, a number of hemolytic and nonhemolytic streptococci are fairly resistant to neomycin, and this drug is also quite ineffective against Shigella organisms. It is in these three vital areas of deficiency that neomycin receives powerful support from the sulfonamides. The broad-spectrum qualities of neomycin call for watchfulness against staphylococcal entero-colitis.

Finally, it has yet to be demonstrated that radical suppression of the bacterial flora of the gastrointestinal tract is necessary or desirable in gut surgery. Many years of experience have shown that "sulfonamide preparation" of the gut produces very satisfactory results, with minimal risk to the patient. It would seem, therefore, that the efficiency and safety of poorly absorbable sulfonamides should make them the drugs of choice as chemoprophylactics in bowel surgery of the aged.

## SUMMARY

Chemotherapy in the older age group is not essentially different from that at any other age. However, the changes in the host induced by the physiologic aging process and the trauma of chronic or repeated intercurrent disease, call for greater care in the administration of potentially dangerous agents and for a more judicious selection of chemotherapeutic drugs. This means weighing the seriousness of the disease and the potency of the selected agent against the increasing risk of drug toxicity and possible complications in patients past the prime of life.

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# NEWER CLINICAL AND LABORATORY STUDIES IN THE AGED

## VI. Serum Lipids, Lipoproteins and Atherogenic Index in "Normal" Subjects 80–100 Years of Age*

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The term "arteriosclerosis" refers to several distinct pathologic entities producing thickening of the blood-vessel wall. It embraces such conditions as atherosclerosis, Mönckeberg's sclerosis, arteriolosclerosis, and hyperplastic arteriosclerosis. Recent investigations have been most numerous in the field of the etiology and pathogenesis of atherosclerosis, since among the arteriosscleroses in man this is the lesion which is the chief cause of morbidity and mortality (1).

Numerous attempts have been made to develop a biochemical procedure for prognosis and diagnosis in this insidious condition. An elevated level of serum cholesterol (2–4), abnormalities of lipid fractions (5), an abnormal ratio of cholesterol to phospholipid (6, 7), and a qualitative disturbance of serum lipoprotein fractions have all in turn been pointed to as the important factor (8, 9). It is, however, becoming increasingly obvious that no one single factor is significant.

It is important to realize that a complete separation of so-called atherosclerotics from normal subjects cannot be expected with the present biochemical methods. Whether or not the determination of lipoprotein molecules and the calculation of an atherogenic index, as reported by Gofman *et al.* (10–12), will provide us with a guide for the diagnosis and therapy of atherosclerosis, is still to be substantiated.

Gofman and his associates (13–15) have been engaged in the systemization of lipoprotein interrelationships in sera of patients with atherosclerosis. They have employed the analytical ultracentrifuge, by which such lipoproteins are measured as to a type and concentration during the process of flotation. The flotation rates are expressed in Svedberg units (Sf). A Svedberg unit is considered to be $1 \times 10^{-13}$ cm./sec./dyne/Gm. Apparently lipoproteins from Sf 40,000 to Sf 2 are metabolically interrelated. This is suggested by Lindgren, Nichols and Freeman for the serum of aged persons (16).

The purpose of the present investigation was to determine variations and interrelationships of Sf 0–400 lipoprotein and lipid fractions, as well as the atherogenic index and distribution curves. To date, such data have not appeared in the literature.

* Aided by a grant from the Sophie D. Cohen and William W. Cohen Foundation.

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## METHODS AND MATERIAL

The study was undertaken on 36 men and 39 women between the ages of 80 and 100 years (average, 86 years). These individuals were confined to a hospital for chronic diseases, mainly for economic and social reasons. Most of patients were ambulatory or semiambulatory. None had a previous history of diabetes, coronary artery, liver or venereal disease, or other major illness.

From each fasting patient was withdrawn 30 ml. of venous blood, which was permitted to clot at room temperature. A 20-ml. portion of blood was utilized for the measurement of the Sf lipoprotein molecules of varied classes, such as Sf 0–12, Sf 12–20, Sf 20–100 and Sf 12–400. The remainder of the blood was used for determination of the concentration of serum cholesterol (free, esterified, and total), using the Schoenheimer and Sperry method (17); lipid phosphorus, using the Youngburg method (18); and total lipids, using the gravimetric method (19). Counts were made on peripheral blood, in order to exclude marked anemia. Blood sugar, creatinine and nonprotein nitrogen values were obtained, to exclude conditions produced by a high renal threshold.

## RESULTS

### Lipid fractions

*Total lipids.* In each age group, the range was greater in females than in males. The mean values were higher for females than males, being 645 mg. and 611 mg. per 100 ml., respectively (Table 1 and Fig. 1).

*Total cholesterol.* The values were higher in females than in males, with an average of 230 mg. and 203 mg. per 100 ml., respectively (Table 1 and Fig. 1). This difference was found to be statistically significant on the basis of the standard *t*-test ($p$ less than 1 per cent).

*Cholesterol esters.* The values were higher for females than for the males, with a mean average of 161 mg. and 126 mg. per 100 ml., respectively. This is within the normal percentage of the total cholesterol value—70 per cent for females and 62 per cent for males.

*Free cholesterol.* The average for females was 69 mg. and for males, 77 mg. per 100 ml. This represents a proportion of 30 per cent for females and 38 per cent for males, as part of the total cholesterol partition (within normal range).

*Phospholipids.* The values in females were not as constant as in males. In males the average was 194 mg., and in females 192 mg. per 100 ml. This difference was found statistically not significant on the basis of a standard *t*-test ($p$ greater than 5 per cent). (Table 1 and Fig. 1.)

*Neutral fats.* The arithmetic mean values for females was 264 mg., and for males 196 mg. per 100 ml.

*Ratio of phospholipids to total cholesterol.* The ratio was less than 1.00 in both the female and male groups. The mean value was 0.83 for females and 0.95 for males (Table 1 and Fig. 1). This difference in the P/C ratios was due to the higher total cholesterol values in the males. As mentioned in previous observations, the ratio of the phospholipids to cholesterol at the critical level of 1.00

TABLE 1

*Arithmetic Mean, Standard Deviation, and Coefficient of Variation of the Serum Lipid Partitions, Lipoprotein Molecules, and Atherogenic Index in "Normal" Subjects, Aged 80–100 Years*

| | A Mean (mg. per 100 ml.) | | B Standard Deviation* (mg.) | | C Coefficient of Variation† (per cent) | |
|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female |
| Lipid Fractions | | | | | | |
| Phospholipids | 194 | 192 | 31.0 | 32.7 | 16.1 | 17.2 |
| Total cholesterol | 203 | 230 | 41.1 | 31.3 | 20.4 | 13.7 |
| Cholesterol esters | 126 | 161 | 26.9 | 28.5 | 22.7 | 18.2 |
| Free cholesterol | 77 | 69 | 16.5 | 20.8 | 23.5 | 31.0 |
| Neutral fats | 196 | 264 | 98.7 | 88.0 | 50.3 | 33.3 |
| Total lipids | 611 | 645 | 77.9 | 187.5 | 12.8 | 30.1 |
| Ratio phospholipids to total cholesterol (units) | 0.95 | 0.83 | 0.14 | 0.14 | 14.4 | 18.5 |
| Lipoprotein Molecules | | | | | | |
| Sf 0–12 | 293 | 305 | 68.7 | 80.2 | 23.6 | 26.5 |
| Sf 12–20 | 36 | 43 | 14.5 | 17.0 | 40.5 | 40.0 |
| Sf 20–100 | 43 | 46 | 22.5 | 30.9 | 52.8 | 67.8 |
| Sf 12–400 | 131 | 128 | 60.0 | 67.8 | 46.2 | 53.5 |
| Atherogenic Index (units) | 53.0 | 53.2 | 11.3 | 16.5 | 21.5 | 31.3 |

* S.D. $= \sqrt{\frac{\text{sum of squares of observations}}{\text{number of observations}} - (\text{mean of observations})^2}$.

† Coefficient of variation $= \frac{\text{estimated S.D.‡}}{\text{arithmetic mean}} \times 100$ (in percentage form).

‡ Estimated S.D $=$ S.D. $\sqrt{\frac{\text{observations}}{\text{observations} - 1}}$.

cannot always be considered as evidence of atherosclerosis (20–23). Such a variance in ratio values cannot be very significant and is surely not caused by sex differences. It may reflect variable lipid concentrations (24).

## Lipoprotein molecules

*Sf 12–20 lipoprotein molecules.* The arithmetic mean value for Sf 12–20 molecules was 43 mg. per 100 ml. for females, and 36 mg. per 100 ml. for males. The decreased values for Sf 12–20 molecules in both sexes were concomitant with a decrease in the total cholesterol and phospholipid values (Table 1 and Fig. 1).

*Sf 20–100 lipoprotein molecules.* In general the values for these molecules were higher in the females (46 mg. per 100 ml.) than in the males (43 mg. per 100 ml.) (Table 1). The levels of Sf 12–20 and Sf 20–100 molecules tend to be much higher in females than in males with advancing years.

*Sf 0–12 lipoprotein molecules.* The arithmetic mean values for males and females were, respectively, 293 and 305 mg. per 100 ml., showing a slight increase for the female group.

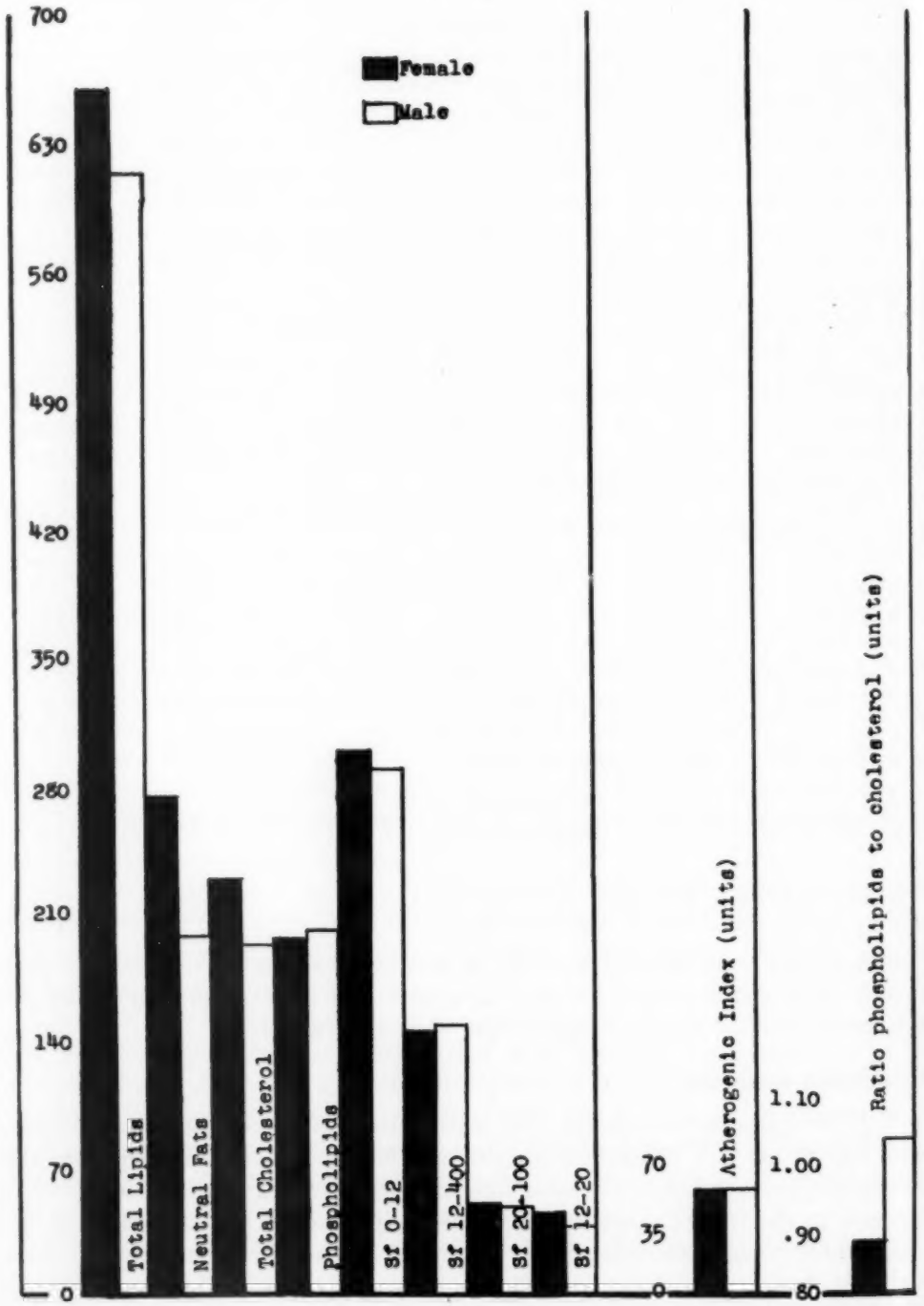


FIG. 1. Histogram showing mean values of serum lipid partitions and lipoprotein molecules Sf 0-400. Values are expressed in mg. per 100 ml. of serum. Atherogenic index and ratio of phospholipids to cholesterol are expressed in units. "Normal" male and female subjects 80–100 years of age.

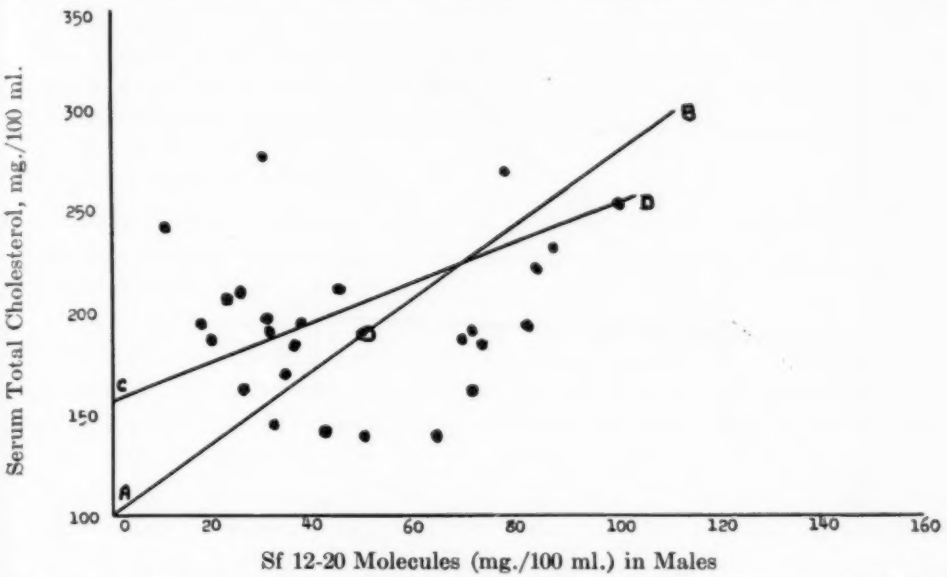


FIG. 2. Scattergram with mean value (A-B) and regression line (C-D) showing a significant positive correlation between the level of serum total cholesterol and Sf 12-20 molecules in "normal" men aged 80–100 years. Regression coefficient (.996). Significant at the 99 per cent level. ($p < .01$).

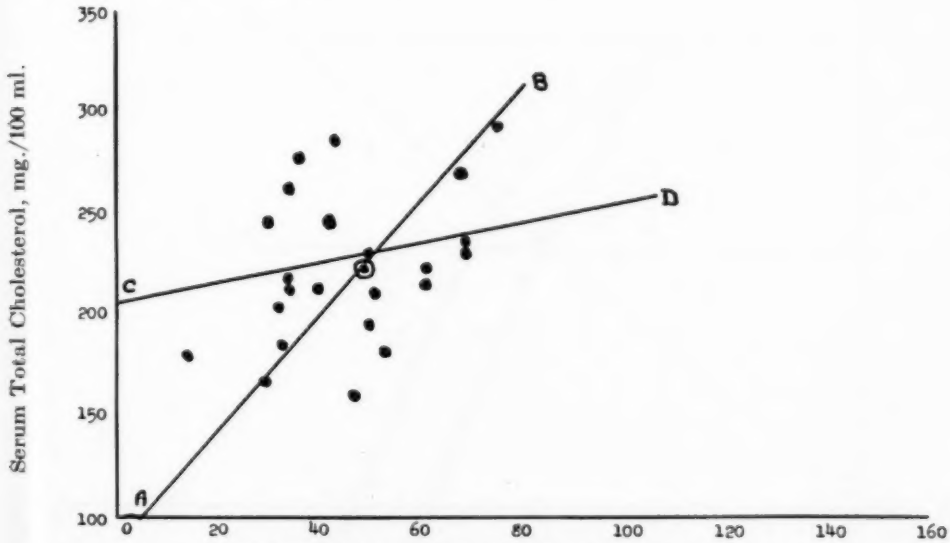


FIG. 3. Scattergram with regression line (C-D) showing a significant positive correlation between the level of serum total cholesterol and Sf 12-20 molecules in "normal" females, aged 80–100 years. Regression coefficient (.52). Significant at the 99 per cent level. ($p < .01$). A-B, arithmetic mean values.

*Sf 12–400 lipoprotein molecules.* The values were practically the same in both the male and female groups. The slight increase for the male group is of no significance.

*Total cholesterol versus Sf 12–20 and 20–100 molecules.* The relationship be-

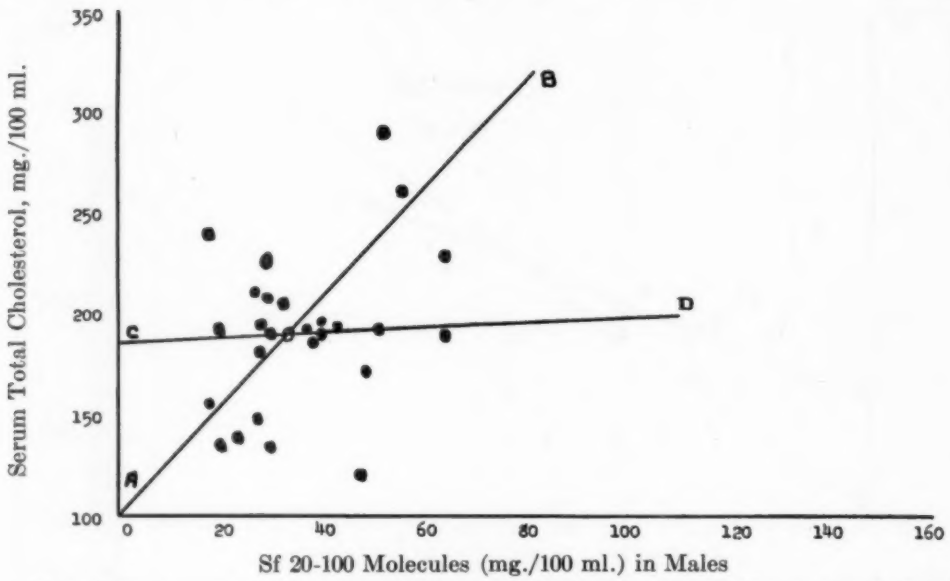


FIG. 4. Scattergram with regression line (C-D) showing no significant correlation between the level of serum total cholesterol and Sf 20-100 molecules in "normal" male subjects, 80–100 years of age. Regression coefficient (.127). Not significant at the 95 per cent level. ($p > .05$). A-B, arithmetic mean values.

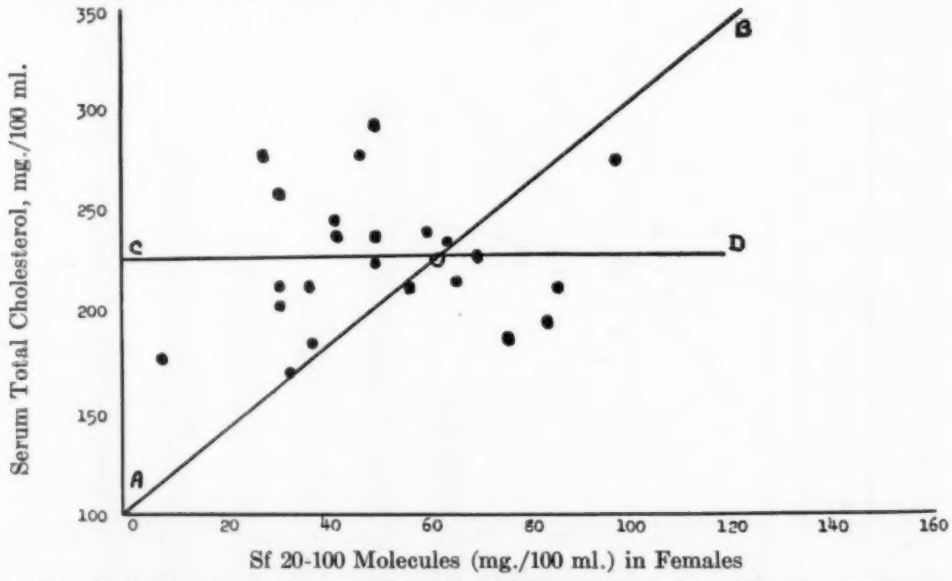


FIG. 5. Scattergram with regression line (C-D) showing no significant correlation between the level of total serum cholesterol and Sf 20-100 molecules in "normal" female subjects, aged 80–100 years. Regression coefficient (.041). Not significant at the 95 per cent level. ($p > .05$). A-B, arithmetic mean values.

tween the concentrations of total cholesterol and the Sf 12–20 and Sf 20–100 molecules was analyzed. This was accomplished by taking a linear regression of (X) on (Y). The resulting regression lines are shown in Figures 2, 3, 4 and 5. The strengths of the exhibited relationships were tested by applying a standard

*t*-test to each of the regression coefficients. The regression lines show a correlation between the level of total cholesterol and that of Sf 12–20 molecules, but not of Sf 20–100 molecules, in both males and females.

*Frequency curves of Sf molecules*

In interpreting frequency curves the observer is concerned with the relative steepness (which is indicative of low variability or small range) as opposed to relative flatness (which is indicative of increased variability).

*Sf 12–20 lipoprotein molecules* (males and females, Fig. 6). Regarding frequency, the curves show that there was equal variability in both groups; the average for females was greater than that for males. The distribution in the female was greater than in the male. The 50 per cent point in the females fell at the level of 45–50 mg. per 100 ml., and in the males at 34–35 mg.

*Sf 20–100 lipoprotein molecules* (males and females, Fig. 7). The males showed greater variability over a larger range. The curve for females was steeper than that for males, suggesting greater concentration. The 50 per cent point fell at the level of 40–42 mg. per 100 ml. in the males and at 45–50 mg. in the females.

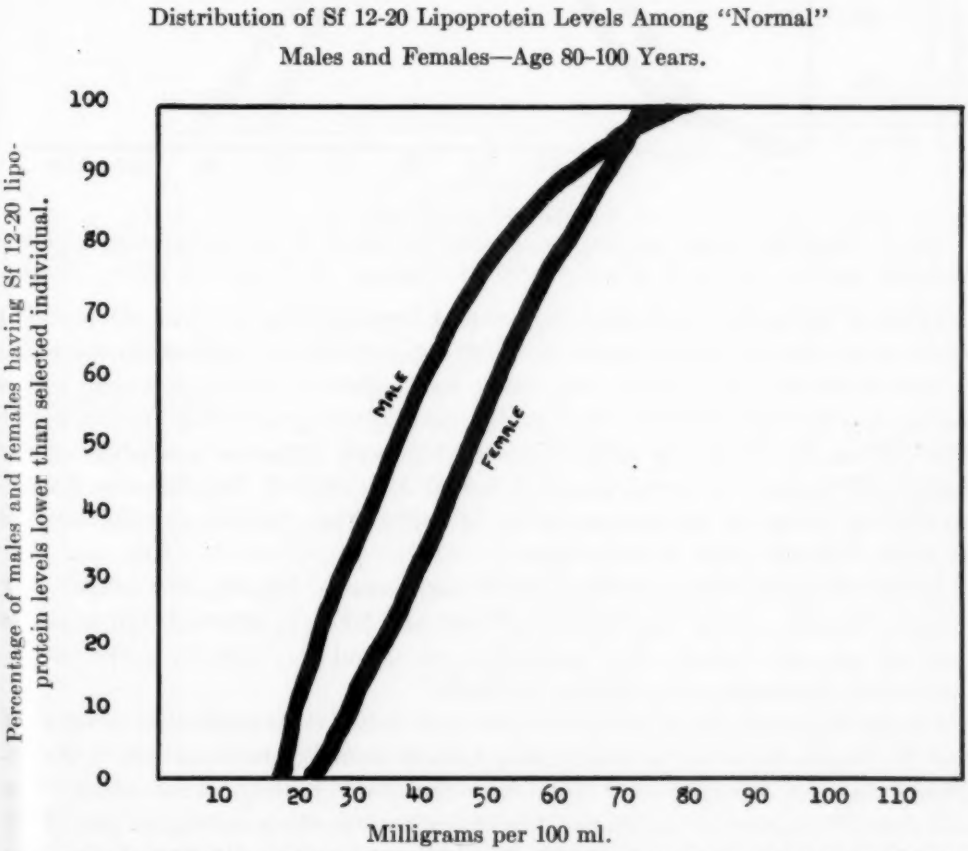


FIG. 6. Sf 12-20 lipoprotein level of selected individual. At 50 per cent level, Sf 12-20 molecule falls at 45–46 mg. per 100 ml. (females) and 34–35 mg. per 100 ml. (males).

Distribution of Sf 20-100 Lipoprotein Levels Among "Normal" Males and Females—Age 80–100 Years.

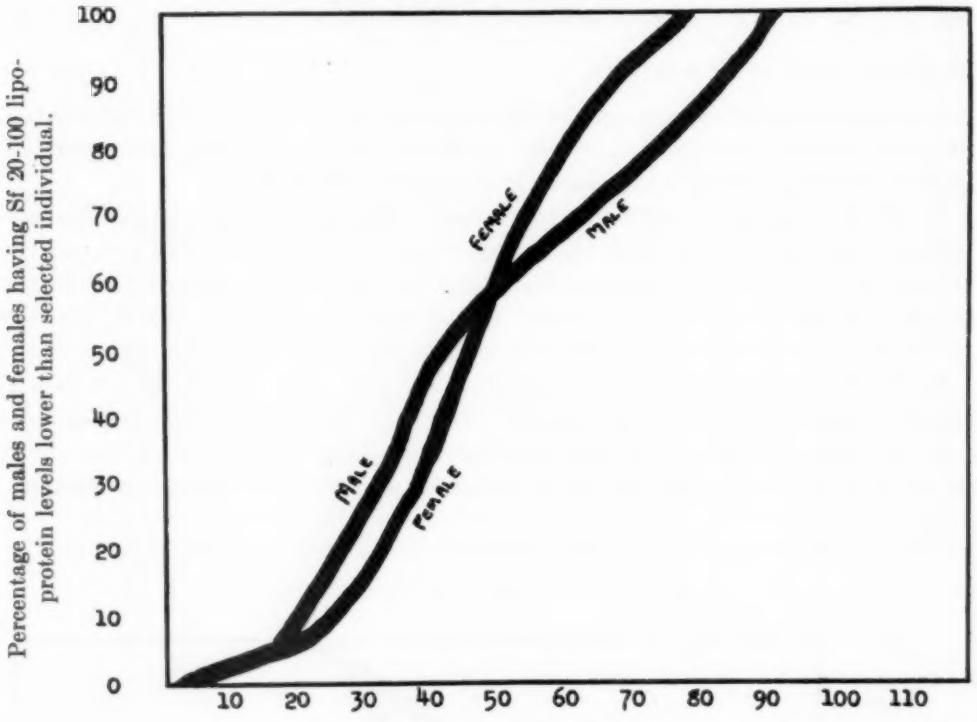


FIG. 7. Sf 20-100 lipoprotein level of selected individual. At the 50 per cent level, the Sf 20-100 molecule falls at 45–46 mg. per 100 ml. (females) and 40 mg. per 100 ml. (males).

*Sf 0–12 lipoprotein molecules* (males and females, Fig. 8). The 50 per cent point in the females fell at the level of 310 mg. per 100 ml., whereas in the males it was at 290 mg. The 50 per cent point was higher in the females than in the males, and the variability in the females was slightly greater than in the males. The difference was in the same direction for both ranges of molecules in the males and females. In the curves of both Sf 0–12 and Sf 12–20 molecules (Figs. 6 and 8) the levels for females tended to be higher than those for males, but the medians were the same in both sexes.

*Sf 12–400 lipoprotein molecules* (males and females, Fig. 9). The 50 per cent point in females was at the level of 160 mg. per 100 ml., whereas that in males was 140 mg. per 100 ml. The variability was about the same in males and females, but the median was higher in females.

*Comparison of Sf 12–20 and Sf 20–100 distribution curves with those of Sf 0–12 and Sf 12–400.* Most of the distribution curves tended to be double or bi-modal. There was no homogeneous area and the data indicate that there were two distinct classes of substances directly related to their molecular size. With the newer (10–12) standard classification (Sf 0–12 and Sf 12–400) there was a tendency toward a more definite bi-modal distribution (except Sf 12–400 in

Distribution of Sf 0-12 Lipoprotein Levels Among "Normal" Males and Females—Age 80–100 Years.

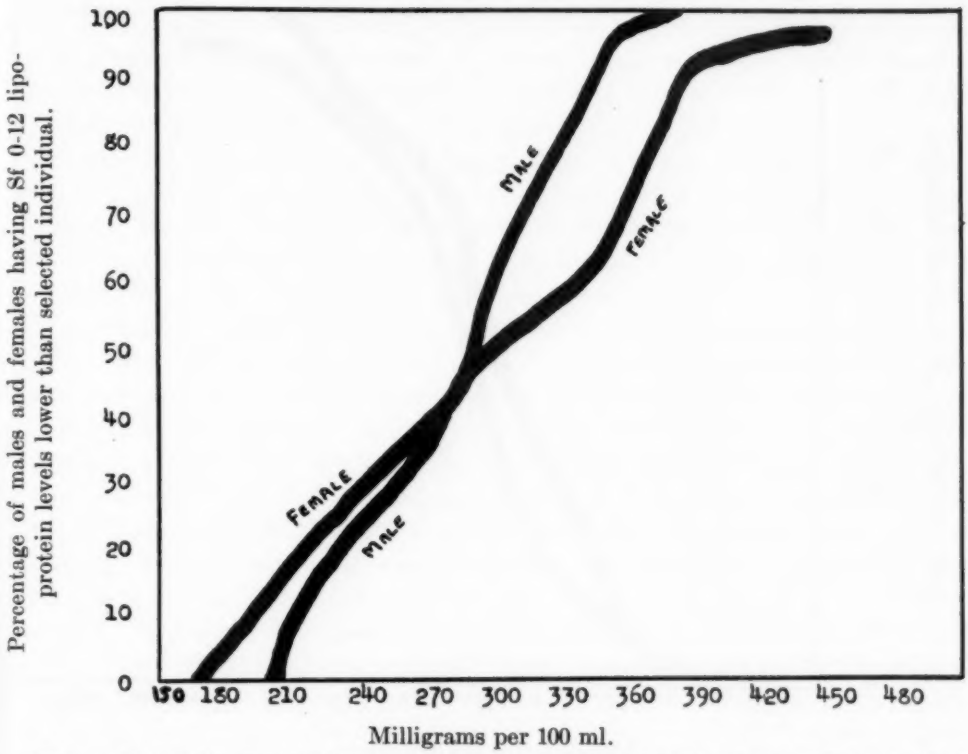


FIG. 8. Sf 0-12 lipoprotein level of selected individual. At the 50 per cent level, the Sf 0-12 molecule falls at 310 mg. per 100 ml. (females) and 290 mg. per 100 ml. (males).

females) than with the older classification (Sf 12–20 and Sf 20–100). In general, however, both the old and new curves were comparable.

### Atherogenic index

This index of coronary atherogenicity is obtained by multiplying the value (in mg. per 100 ml.) for Standard Sf 0–12 plus 1.75, by the value for Standard Sf 12–400, and dividing arbitrarily by 10. The result is expressed in units.

In our series the average atherogenic index of 53.0 units was the same for both males and females. This is significantly lower than the index found in younger age groups (10–12) (Table 1 and Fig. 1).

## DISCUSSION

There has been a great deal of interest in atherosclerosis and coronary artery disease, both by the general public and the medical profession. The finding of such pathologic lesions in younger individuals since World War II (25) and the Korean War (26) suggests that atherosclerosis is not a process of aging.

A previous publication on serum lipid partitions in males 80–100 years of age (27) showed values which were less than normal. Our present observations

Distribution of Sf 12-400 Lipoprotein Levels Among "Normal" Males and Females—Age 80–100 Years.

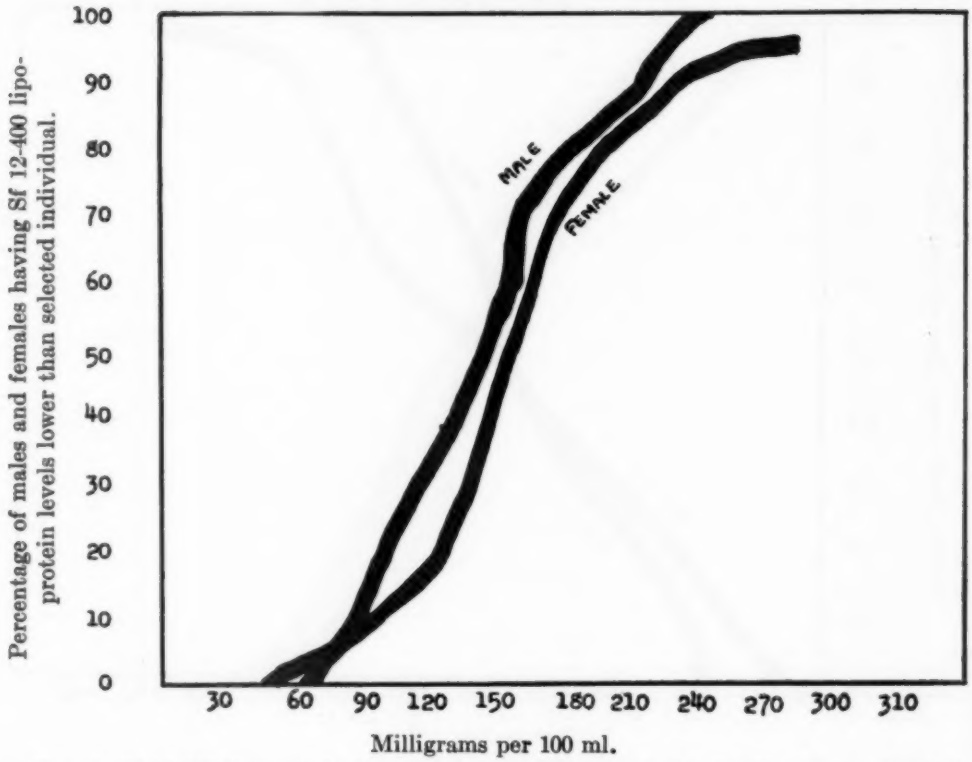


FIG. 9. Sf 12-400 lipoprotein level of selected individual. At the 50 per cent level, the Sf 12-400 molecule falls at 160 mg. per 100 ml. (females) and 140 mg. per 100 ml (males).

are in both males and females 80–100 years of age who were not studied previously, particularly with reference to Sf lipoprotein molecules, frequency curves, and the atherogenic index.

Our studies show a higher value in females for all lipid partitions except neutral fat and an increase in the lipoprotein molecules. These values were less than those encountered previously in the middle-age group (10–12). There was a significant correlation of the total cholesterol levels but not of the phospholipids in both the male and female groups. This observation requires further elucidation, inasmuch as the phospholipids keep the cholesterol in a state of colloidal suspension. There was a significant correlation between the Sf 12–20 molecules and the total cholesterol level in both males and female. This was contrary to the findings of Gertler and Oppenheimer in their female patients (28).

It is obvious that although a substance (lipoprotein) may be closely associated with atherosclerosis, there is no obligation for that substance to be correlated with another substance (cholesterol). This study is fairly good evidence that the cholesterol-atherosclerosis relationship is weak, and that it lacks significant contribution from the lipoproteins which themselves correlate very little, if any, with the level of cholesterol (29).

In our series of 75 patients we attempted to avoid the error of presenting results or conclusions on the basis of small, statistically insignificant age groups. It would be misleading to classify our patients into more than one group, aged 80–100 years (other factors, except sex, being constant for the entire group). When on the basis of greater numbers of patients, further data are compiled, only then can the 80–100 year group be broken down into subdivisions.

The mean values in females compared to those in males were as follows: total lipids, 645 and 611 mg. per 100 ml.; total cholesterol, 230 and 203 mg.; free cholesterol, 69 and 77 mg.; esterified cholesterol 161 and 126 mg.; phospholipids 192 and 194 mg.; and neutral fats 264 and 196 mg. per 100 ml. For the most part, the values were higher in females.

*Relationship of cholesterol to lipoprotein molecules.* In our particular age group of 80 to 100 years, the total cholesterol level in females was higher than that in males. This difference was found to be statistically significant on the basis of the standard *t*-test ($p$ less than 1 per cent). Our figures were lower than those for younger groups with an average age of 46 years (30). In males and females, on the basis of the *t*-test, at the 99 per cent level, there was a significant relationship between Sf 12–20 lipoproteins and the total cholesterol values ($p$ less than 1 per cent). This is in precise agreement with the data of Gofman in his studies with people below 70 years of age.

It has been shown by numerous observers, as well as the authors (22), that hypercholesterolemia is not a constant finding in patients afflicted with atherosclerosis and chronic coronary artery disease. Patients with coronary disease may have a normal cholesterol level and still have a very high Sf 20–100 value. With the exception of acute myocardial infarction (20, 23), in none of the entities reported thus far are there marked abnormalities of the serum cholesterol level.

*Standard Sf 0–12 and Sf 12–400 lipoprotein classes.* With increased technical skill in improving analytical procedures in the determination of the flotation rates of lipoproteins, a modified classification of the lipoprotein groups has been established. These new standard classes are Sf 0–12 and Sf 12–400. In an attempt to make maximal use of the quantitative possibilities in the analytical ultracentrifuge approach to the problem of atherosclerosis, precise weighting factors for the various lipoprotein classes were established.

It is stated that an ideal compendium of the pertinent information on lipoprotein would be a single number descriptive of an individual's coronary atherogenic potentialities, or rate of development of coronary atherosclerosis. This value is referred to as a criterion for coronary atherogenicity and is termed the atherogenic index (12).

It is most interesting that the average *atherogenic index* in our series was 53.0 units for both males and females, aged 80–100 years. This is significantly lower than the index found in younger age groups (10–12). Whether or not the atherogenic index is low because this age group of patients has less tendency to atherogenesis, or whether there is less tendency to atherosclerosis because of the higher survival rate, cannot be answered at this time.

Values for total serum lipids, standard Sf lipoprotein molecules and the ather-

ogenic index rise steadily, in both males and females from age 20 until approximately 65–75 years, after which there is a steady decline until the age of 100. There seems to be a "threshold" between the ages of approximately 65 and 75 years. Cholesterol and phospholipid levels show no significant changes (31, 32).

There does not appear to be a close relationship between the ratio of alpha to beta lipoproteins (obtained by paper electrophoresis, using Oil Red O) and the Sf lipoprotein values obtained on the same sera by the analytical ultracentrifuge method (33).

*Distribution curves.* The distribution curves for lipoproteins, published for the first time for the 80–100 year group, were determined both for the older and the newer classification (Figs. 6–9). Our results show that the curves in all classes are comparable. All the distribution curves show the values in females to be greater than those in males, which is also the case with regard to total cholesterol levels. This does not necessarily infer that the same predictions concerning atherosclerosis may be made from cholesterol data as from lipoprotein data (Fig. 1). The cause of higher values in females still needs explanation. Various observers have attempted to explain the differences on the basis of endocrinologic make-up, and have administered estrogenic substances intravenously, in humans (34, 35) and in chicks, in an attempt to shift lipoprotein patterns (36). This work is still inconclusive and further data must be collected. It is well established that females have less tendency to coronary atherosclerosis than males in the fourth decade of life. In our study, we attempted to preclude conditions which may alter lipoprotein values, such as abnormalities of constitution and serum lipid values, obesity, malnutrition and hormonal disturbances (37).

Use of the newer standard classification (Sf 0–12 and 12–400) tends to show a more definite bi-modal distribution (Figs. 8 and 9).

## SUMMARY AND CONCLUSIONS

1. Lipoprotein fractions (Sf 0–400), distribution curves and atherogenic index have been determined for the first time in "normal" subjects, aged 80–100 years.

2. Levels of serum lipids (cholesterol, lipid phosphorus, total lipids and neutral fats) and phospholipid-to-cholesterol ratios are less at age 80–100 than in the middle-age group.

3. Serum total cholesterol and total lipid values are significantly higher in females than in males.

4. The ratio of phospholipids to total cholesterol is statistically unreliable as an aid in biochemical diagnosis of atherosclerosis.

5. In both males and females there is a correlation between the level of total cholesterol and that of Sf 12–20 lipoprotein molecules, but not of other fractions.

6. A low serum level of cholesterol may exist concurrently with a high level of standard lipoprotein fractions.

7. Distribution curves for all classes of lipoprotein molecules (Sf 0–12, 12–20, 20–100 and 12–400) are comparable.

8. Distribution curves show lipoprotein values to be greater in females than in males in the 80–100 year group.

9. The recently designated standard Sf 0–12 and 12–400 lipoprotein molecules

may provide more accurate criteria in the diagnosis of atherosclerosis, as shown by the bi-modal character of their respective distribution curves.

10. The atherogenic index for the 80–100 year age group is the same in both males and females, but is significantly lower than the index for younger age groups of both sexes.

11. There seems to be a "threshold" at approximately 65–75 years of age, after which there is a decline in the values for total serum lipids, lipoprotein molecules, and atherogenic index.

12. Distribution curves for various groups of lipoprotein molecules may eventually set the diagnostic and treatment pattern for atherosclerosis.

*Acknowledgments*

The authors are grateful to Dr. Linn J. Boyd, Professor of Medicine, New York Medical College, Flower and Fifth Avenue Hospitals and Director of Medicine of its allied Hospital Divisions, and to Dr. John W. Gofman of the University of California, for personally discussing our findings and for many invaluable suggestions. We also wish to express our thanks to Drs. Robert Coleman Batterman and Alfonso A. Lombardi for permission to study the patients on their services; to Dr. Julius Pomeranze for his aid in procuring blood specimens; to Dr. Allan Birnbaum, Director of Statistical Consulting Service, Columbia University; and to our secretary, Miss Zelda Forman.

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# EFFECTS OF LIPOTROPES AND SITOSTEROL ON THE LEVEL OF BLOOD LIPIDS AND THE CLINICAL COURSE OF ANGINA PECTORIS*

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It seems safe to assume that hypercholesterolemia, per se, is not the cause of atherosclerosis. On the other hand, we cannot question the fact that cholesterol is intimately associated with the problem of atherogenesis (1).

Gubner and Ungerleider (2) have shown that there is little correlation between atherosclerosis and so-called normal variations in the concentration of blood cholesterol. They have also pointed out that when individuals with extremely low blood cholesterol levels are compared with those with definitely elevated levels, there does appear to be some correlation as to the degree of atherosclerosis.

In order to test this observation by long-term, controlled experiments, my associates and I have been interested in finding some substance that would decrease the blood cholesterol concentration in the normal individual as well as in those with hypercholesterolemia, whether of the familial or secondary type.

We have tried many substances, but have not been able to achieve our purpose to date. Today I shall present data from our most recent failures.

## LIPOTROPES

Lipotropic agents have been used by many investigators, with variable results. These studies are complicated by many factors. Among them are:

1. Spontaneous fluctuations of the level of blood lipids,
2. Diarrhea,
3. Anorexia with weight loss,
4. Constipation.

Diarrhea and weight loss may decrease the cholesterol level, whereas constipation may increase it or obscure a decrease that would be noticeable if the bowel movements were regular. Davison (3), in a detailed review of this field, has pointed out many problems in experimental design which would complicate most of this work.

### *Methods*

In our work with lipotropic agents, we used a mixture of choline and inositol with cherry syrup and chose patients with angina pectoris as our subjects. Patients with angina pectoris (myocardial ischemia) were chosen, rather than survivors of myocardial infarction, for the reason that the pain produced by ischemia can be relieved by nitroglycerin. Other things being equal, the amount

* Presented before the Graduate Symposium on Geriatric Medicine, given by the American Geriatrics Society, New York, N. Y., November 12 and 13, 1954.

of pain which the patient experiences tends to reflect the degree of coronary insufficiency. This can be further checked by the number of nitroglycerin tablets which the patient takes daily.

In Figure 1 is shown a report card modified from that proposed by Greiner (4), which was used in this study. Our modification consisted of the addition of one column showing the number of nitroglycerin tablets the patient had taken each day. The patients were instructed to make two entries on the card each night before retiring: 1) an estimate of the relative amount of pain experienced that day, and 2) the number of nitroglycerin tablets taken. Each card covered a three-week period, which was the interval between the patient's visits. These patients were selected from the Fourth Medical (N.Y.U.) Cardiac Clinic of Bellevue Hospital and were fitted into a randomized series, so that for six months they would take the drug being tested and for six months take a placebo which consisted of a cherry-syrup vehicle containing 25 cc. per liter of concentrated hydrochloric acid. The taste of the two preparations was almost identical, and when the subject was switched from drug to placebo or vice versa, he was given a mixture of the two preparations for three weeks in order to lessen any suspicion he might have that his medication had been changed. Our program was six months of either drug or placebo, three weeks of a mixture, and then six months of either placebo or drug. In this way, the patient could act as his own

**DAILY REPORT CARD**

*For Securing Data on Cardiac Pain in Patients with Angina of Effort.*

BRING THIS CARD TO CLINIC NEXT VISIT

*How much pain in the heart did you have each day?*

| DAY OF THE WEEK | SAME HEART PAIN AS USUAL | LESS HEART PAIN THAN USUAL • GOOD DAY | MORE HEART PAIN THAN USUAL • BAD DAY | NO HEART PAIN AT ALL | NUMBER OF PAIN TABLETS TAKEN TODAY |
|---|---|---|---|---|---|
| *Sunday* | | | | | |

*Before going to bed, each day, write a mark (X) in the space that describes your heart pain for the entire day.*

FIG. 1. Example of card used to record daily data on patients with angina pectoris. (Reproduced with permission from Jackson, Wilkinson, Meyers, Bruno and Benjamin: An evaluation of the effect of choline and inositol on the clinical course and serum lipids in patients with angina pectoris, *Ann. Int. Med.* **42:** 583 (Mar.) 1955.) (5).

control and, at the same time, groups of drug and placebo patients could be compared.

*Results*

Sixty-three patients were started on this project, but 23 are not included in our final data because they failed to complete at least four months of treatment with either the drug or the placebo.

Because all of the remaining 40 subjects were not under identical regimens, they were divided into two groups. Group I included patients who had taken both drug and placebo for at least four months. Group II included those who had taken either drug or placebo for at least four months.

To permit a more critical analysis, Group I was further separated into two subgroups, A and B. Four subjects with "cardiac interruption" were excluded from the main analysis (Group I A). One patient, who had an episode of congestive failure early in his course, was included in this group by starting his period of observation after he returned to the project. Of the remaining 23 patients in

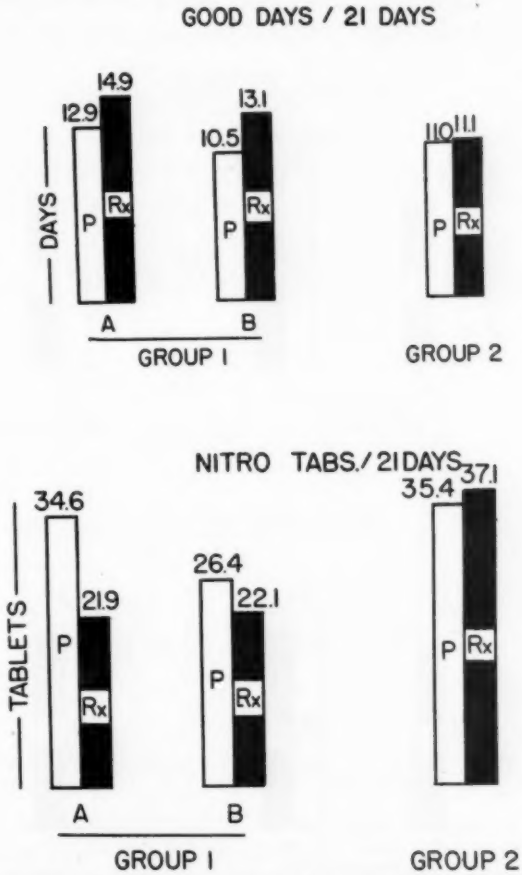


FIG. 2. Clinical response in patients receiving lipotropic drug (Rx) compared with that in patients receiving placebo (P). The values at the tops of the columns are the number of good days (upper graph) or tablets taken (lower graph), respectively, per twenty-one days.

Group I, 15 had been treated in the drug-placebo sequence and 8 in the placebo-drug sequence. Because the full anaylsis required an equal number in each sequence, 8 of the drug-placebo group were selected for Subgroup A in such a way as to include as many subjects as possible with an uneventful, uninterrupted record. The remaining drug-placebo patients, and the 4 "cardiac interruption" patients were included in Subgroup B.

The term "good day" was defined as one for which the subject reported "less pain than usual" or "no pain." Figure 2 shows the number of good days during administration of drug as against placebo, as well as the number of nitroglycerin tablets taken for each of the groups. It may be seen that there was a slightly greater number of good days and a slight decrease in the number of nitroglycerin tablets used, during administration of the drug as compared to the placebo. Analysis of variances as calculated by the F test showed that the probability of this difference appearing by chance was more than 1 in 50. We do not consider this statistically significant. Furthermore, on a 21-day basis, the main differences between groups in favor of the drug seem of little clinical importance.

At each three-week interval, blood was drawn from the patient and analyzed for cholesterol and phospholipid. These data are presented in Figure 3 and it

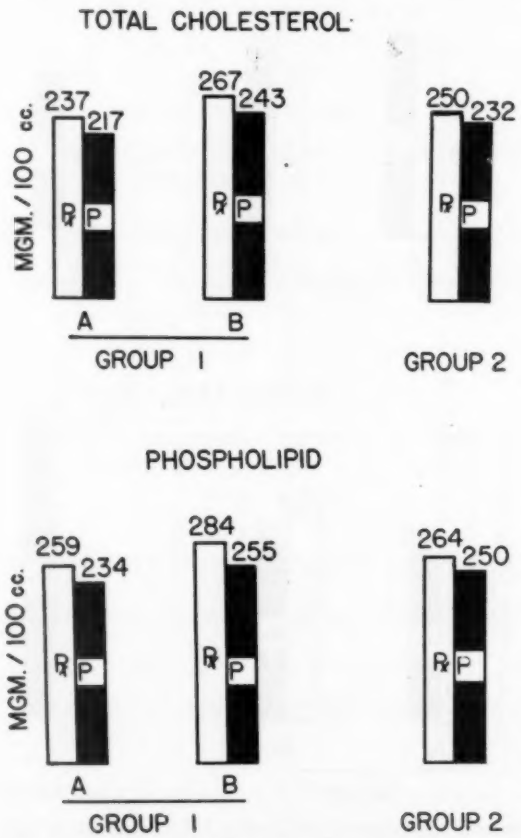


FIG. 3. Effect of lipotropic drug *vs.* placebo on serum cholesterol and phospholipid levels. The values at the tops of the columns are the concentrations per 100 cc. of serum.

may be seen that the cholesterol and phospholipid concentrations are slightly higher in the treated groups than in the untreated group. The difference in Group I-A is of statistical significance. The phospholipid-free cholesterol ratio showed no significant differences in the drug-placebo comparison.

Time will not permit discussion of all the details of this study, but it will suffice to say that it was a double-blind experiment wherein neither the patient nor the attending cardiologist knew what preparation the patient was receiving. The data were analyzed independently by Dr. Mainland of the Department of Biostatistics of the College of Medicine, New York University. More detailed information is given in another article (5).

## SITOSTEROL

It has been reported that sitosterol reduces the expected increase in the level of blood cholesterol when it is added to the diet of cholesterol-fed rabbits (6). Several investigators (7, 8, 9) have reported that crude mixtures of soy sterol as well as purified beta sitosterol, cause a reduction in the level of blood cholesterol in humans when added to the diet.

We used a preparation of soy sterol which contained 14.6 to 15.0 per cent of what was presumed to be gamma sitosterol (10, 11, 12). The experiment was carried out on a metabolic ward during the initial phase; then the patient was observed on an ambulatory basis. Figure 4 shows the outline of the experiment. During periods C and D, the patient received 30 to 60 cc. of the sitosterol emulsion with each meal, thus ingesting between 15 and 30 grams of soy sterol per

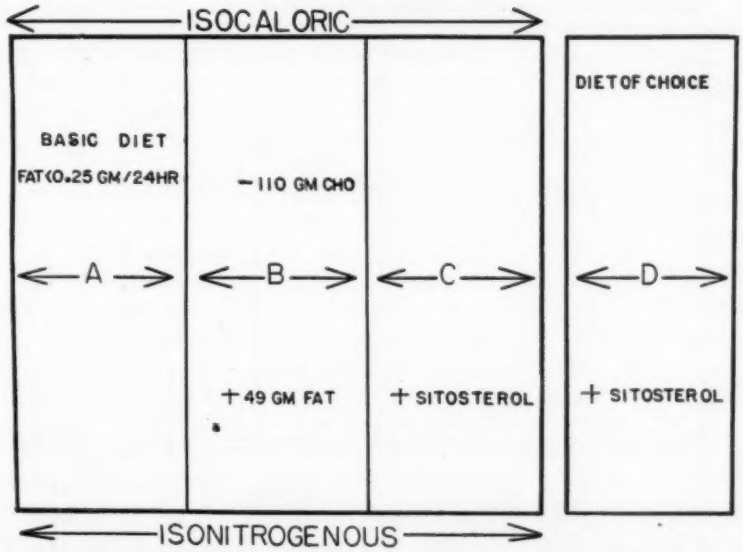


FIG. 4. Schematic outline of experiment, using sitosterol. During periods A, B and C the patients were in a metabolic unit; during period D they were ambulatory. (Reproduced with permission from Wilkinson, Boyle, Jackson and Benjamin: The effect of varying the intake of dietary fat and the ingestion of sitosterol on the lipid and lipoprotein fractions of human serum, *Metabolism* **4**: in press, 1955.) (12).

day. During period C, the diet was controlled, but during period D it was a diet of choice. Data were obtained as to the number of bowel movements each day as well as their consistency. The patients studied had neither diarrhea nor constipation. Of the 7 patients who were started on period A in the metabolic ward, only 4 completed the experiment. In addition, 5 other patients were given sitosterol during the ambulatory phase of the experiment. Figure 5 shows the course throughout the metabolic-ward and ambulatory phases of the experiment in 2

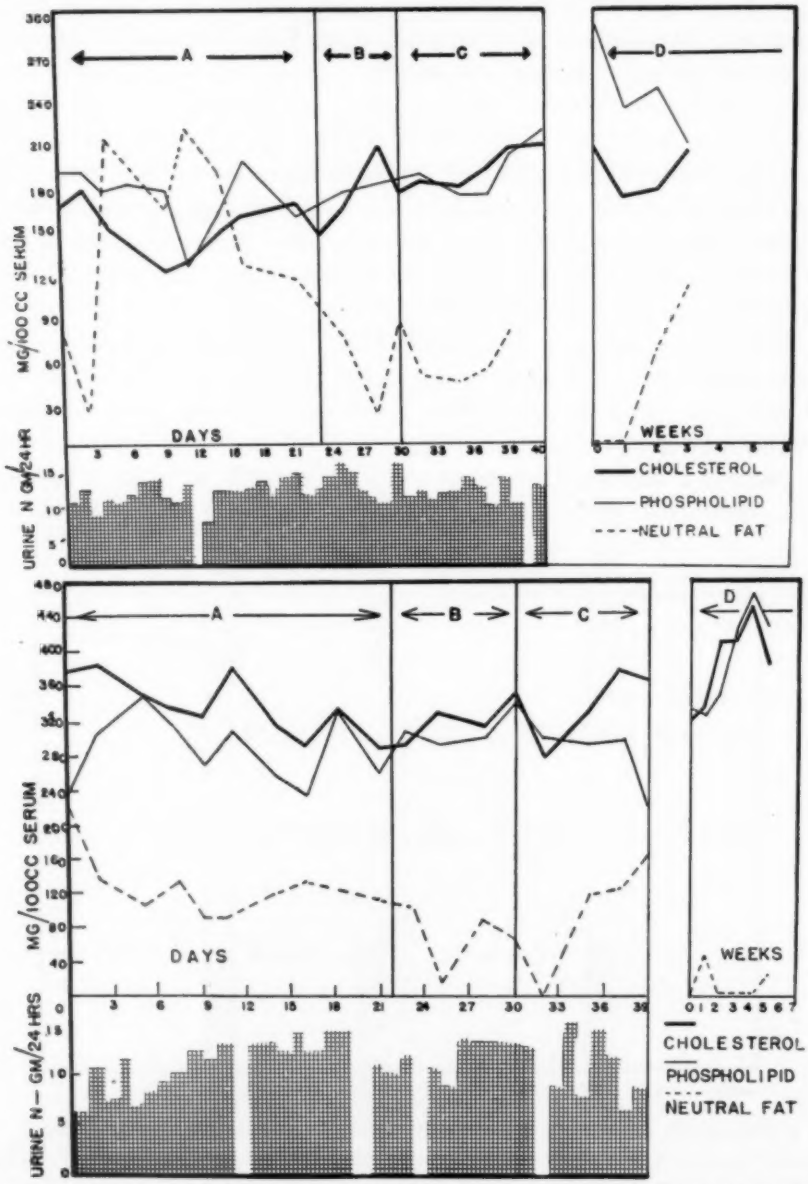


FIG. 5. Effect of sitosterol on serum lipid levels and urinary nitrogen in a patient with normocholesterolemia (above) and in a patient with hypercholesterolemia (below). Periods A and B as in Figure 4. Sitosterol was administered during periods C and D. (Modified from figure to be published also in *Metabolism* (12).)

patients (1 hypercholesterolemic and 1 normocholesterolemic). Altogether, 8 patients taking between 15 and 30 grams of sitosterol per day were followed in the metabolic ward and on an ambulatory basis for periods up to thirty-five weeks without any evidence of a reduction of their serum cholesterol level.

Kinsell (13, 14) has reported variable results, using eight available mixtures of vegetable sterols. Some of these sterols in their crude form produced a moderate reduction in the concentration of serum cholesterol, whereas the same preparations in purified form were ineffectual.

## SUMMARY

In our experience, choline and inositol are not effective agents in reducing the concentration of blood cholesterol. Gamma sitosterol, in preparations available to us, likewise has not been effective.

The fact that there is considerable contradictory evidence as to the value of phytosterols in lowering the blood cholesterol level would suggest that further studies are indicated. Only when phytosterols have been purified and tested separately as well as in combination, will it be known whether or not they have a hypocholesterolemic effect. Many of the "sitosterol" emulsions contain mixtures of beta and gamma sitosterol as well as unknown amounts of stigmasterol.

It is apparent that further studies must be carefully controlled, not only as to the purity of the sterols, but as to the nutritional state of the patient and the mobility of the gastrointestinal tract.

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# RATIONALE OF SEX STEROID REPLACEMENT IN THE "NEUTRAL GENDER"*

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Sex steroid replacement in the aged individual is an extremely controversial subject. If this revolutionary approach to the general physical and mental disabilities associated with the aging process is ever to gain general acceptance from the medical profession, the rationale behind the investigative projects and the techniques employed must be explained satisfactorily, and fully supported experimentally. The complete burden of proof remains, as it should, with the proponents of the concept of "puberty to grave" support with sex steroids.

## THE THIRD SEX

The first efforts to develop a satisfactory steroid replacement technique in the aged were initiated a decade ago (1). The entire project rationale of the last ten years of investigative effort has centered about the essayist's complete conviction that a third sex exists and is rapidly multiplying in our society today. This so-called "neutral gender" is made up of previous members of both the male and female sexes who have reached an approximate age of 60 years.

The entire process of growth, function and retrogression that characterizes physiologic aging in the human mechanism is stimulated or controlled by the glands of internal secretion. In succession, the pituitary, adrenals, thyroid, pancreas, and gonads regulate individual phases of growth, development and function of the various organ systems of the human body. It would be repetitious to outline the well-established contributions of the individual endocrine glands during these growth and function phases. We shall consider in detail, however, the functional potential of the entire humoral system during the degenerative aging phases of the human body, as both male and female components approach the "neutral gender" phase of life.

### *Functional potentials of the gonads*

Apparently, there is no significant reduction in potential function of the pituitary, the adrenals, the thyroid, or the pancreas during the aging process. Evidence is mounting that the gonads are alone in their functional retrogression during the fifth and sixth decades of life. The "neutral gender" age of 60 years is approached by both male and female components with an essentially intact humoral mechanism, if we discount the relatively ineffectual residual function

* Presented before the Graduate Symposium on Geriatric Medicine given by the American Geriatrics Society, New York, N. Y., November 12 and 13, 1954.

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of the gonads. In other words, during our sixties, we are essentially intact from a humoral point of view, and perfectly capable of functioning as efficiently as individual members of much younger age groups, except for the fact that we are essentially castrates. Thus, we have the clear delineation of a third sex or "neutral gender" as we enter the last ten to twenty years of our expected life span.

At the outset, it should be emphasized that the approach to the 60-year marker varies with the two sexes. We are all aware that involutionary changes occur in the female at an earlier average age than in the male. Certainly, there are many women in the process of transfer to the "neutral gender" by the time they reach their fiftieth birthday. Equally certain is the fact that an occasional male reaches and passes his seventieth birthday with no demonstrable evidence of third-sex delineation. Evidently, the average male enjoys a ten-year or even a fifteen-year lag over the female in the phase of gonadal retrogression. Thus, the sixtieth birthday roadmarker should be considered merely a warning or danger sign rather than one of actual mileage.

The short life expectancy of the gonads when compared to the other glands of internal secretion has been discussed clinically for years. Not only do the gonadal influences develop later in life than other humoral forces, but involution of glandular function is first demonstrated by the failing reproductive prowess of the gonads. Essentially, gonadal function is divided into two completely different aspects: first, the propagation of the race through the production of ova and sperm; and second, the support of multiple bodily functions through the production of the sex steroids. The reproductive functions of the gonads are usually even shorter lived than their steroidal functions. The average female has at best twenty-five to thirty years of reproductive life, whereas forty to forty-five years is the average span for the male. In the female, the gonadal rate of decrease in sex steroid production is slower than that of the decrease in reproductive function. In the male, however, the rate of decline in both gonadal functions is frequently about equal. This premature involution of both reproductive cell development and sex steroid production sets the gonads apart from the remainder of the humoral system.

*Clinical and laboratory evidence*

Suggestive and definitive evidence to support the contention of a rapidly developing third gender has been gathered from two distinct sources. Suggestive evidence of the existence of a third sex has been developed by clinical observation. With the approach of the "neutral gender" age, the female pelvic organs shrink in size. The vaginal mucosa becomes atrophic, and the mons loses its full contour. The breasts sag, and girdle-type obesity becomes evident. In the male, body muscle and skin tone are obviously lost. Occasionally there is mild breast development. Facial hair growth slows, and sex interest is retarded.

Definite experimental evidence of the existence of a third sex has grown amazingly during the last year. All of the work is based upon the knowledge that humoral control of our physiologic processes is one of the keys to the prob-

lems of aging. In June 1954, in San Francisco, the American Geriatrics Society was privileged to hear from Starr (2), Gallagher (3) and Tyler (4). In one afternoon the observations of these men (who worked in an entirely unrelated manner) went a long way toward confirming the previously experimentally unsupported contention of the existence of a "neutral gender."

Starr described the investigation of thyroid gland function in aging individuals. He felt that his protein-bound iodine studies had established beyond reasonable doubt that there was no demonstrable evidence of retrogression of the secretory potential of the thyroid gland with advancing years.

Gallagher and Tyler presented equally significant information from an entirely different point of view. Each had data showing well-sustained activity and, even more important, excellent functional potential of the adrenal glands of aging subjects. They could not demonstrate functional disability of the adrenals, even in the 80-year age group. Both of these investigators stated during round-table discussions that they were completely convinced that the adrenal glands of individuals of advanced age were perfectly capable of increased activity should the occasion arise.

As early as 1940, Meyer and Necheles (5) published a complete evaluation of pancreatic activity in the aged. These observers stated that there is a 10 to 20 per cent reduction in effective secretory activity; but, at the functional level described for the aged, this activity is more than sufficient, even for much younger age groups.

Pituitary activity, as measured by follicle-stimulating hormone production, has been investigated in detail in our own laboratory (6). The results demonstrate continued secretory activity, even in the 80-year age group. However, there is a marked reduction from the high post-climacteric levels in both sexes. The continuation of measurable secretory activity suggests a large organ reserve, and perhaps a lack of external stimulation, rather than a functional failure due to the aging process.

Pincus and his associates (7) also have recently confirmed the existence of a "neutral gender" by describing in detail a significant measurable reduction in both the ovarian and testicular function of the aging individual. Thus, the bulk of recent investigative data supports the thesis of a third sex. It is apparent that an essentially castrate population exists today. The gonadal function of this "neutral gender" is either absent or is projected at levels of clinical insignificance.

Why do the gonads alone, of the entire humoral system, fail at such a relatively early age? The failure is not associated with lack of adequate stimulation. The production of follicle-stimulating hormone by the aged pituitary has been described previously. Thus, the essence of failure must be considered to be within the gonad itself. As information accumulates, the impression grows stronger that the fundamental cause for the premature failure of this weak link in the endocrine chain is an inherent lack of functional reserve within the individual gonad.

Suggestive evidence to support this thesis of inherent lack of functional re-

serve in the gonads is found during mature adult life. Both the ovaries and testes are easily reduced to a state of dysfunction during the reproductive years. The gonads are extremely sensitive to the influence of the other elements of the endocrine system. In addition, any general physical disability easily interferes with ovarian or testicular hormone production. It would appear that gonadal activity is not only relatively short-lived, but represents the complete effort of the individual reproductive gland. Unfortunately, as the reproductive activity fails, so also does the sex steroid production. This is the "Achilles heel" of the entire humoral system. If only reproductive activity failed, and sex steroid production was maintained, there would be no slow transfer into the "neutral gender." In that case, replacement therapy would have no role in supportive efforts directed toward the individual's declining years.

## THERAPEUTIC APPLICATIONS

If one accepts the possibility of a third sex in our society, what is to be done about it? This question brings us to consideration of the rationale behind the techniques employed to support the "neutral gender" age groups successfully. Fundamentally, the entire approach to humoral support of the aging population has been to take advantage of the "Achilles heel" of early gonadal involution in the older individual. The various sex steroids, alone or in combinations, have been employed over a ten-year period. Certain basic truths of therapy have been worked out, essentially by the "trial and error" method.

The physical and psychologic results obtained by sustained steroid replacement techniques have been published in detail (8–10) as the work has progressed during the last decade. The regenerative effects on aged individuals, adequately supported for significant lengths of time, must be seen and experienced to be truly believed. Perhaps the psychosomatic aspects have been the most dramatically impressive. It is conservative to say that definite reclamation can be achieved. The tragedy is that, at present, the aged are needlessly allowed to sink to the low level from which sex steroid replacement can reclaim them.

The fortunate results of steroid replacement are still basically dependent for evaluation upon clinical observation rather than laboratory testing. Autopsy study of patients deceased during therapy has produced some interesting results. Recanalization of blood vessels as well as a progressive washing out of calcium from the vessel walls in the target pelvic organs has been described (11).

However, we are at a loss to explain, from strictly a laboratory approach, the significant and sometimes, amazing clinical results observed and previously reported.

### *"All-gender" steroid replacement*

The basic investigative approach has been to achieve success in supportive therapy techniques applied to the members of the third sex who were formerly females, and then to apply these techniques directly to the members who were formerly males. Every effort has been made to simplify methods, to develop an all-gender type of steroid replacement, and to avoid excessive female characteristics such as vaginal bleeding, breast growth, and excessive male-type hirsutism.

The answer to the problem of how best to avoid individual sex characteristics in the "neutral gender" patient and yet provide adequate clinical support, has been to administer a combination of the basic male and female steroids, testosterone and estrogen. The combination that has clinically withstood the test of time in a large number of patients is a 20–1 ratio of testosterone over estrogen. This therapy is at present the direct result of ten years of "trial and error" investigation.

If the 20–1 ratio is maintained in long-range replacement techniques, the undesirable features that either sex hormone exhibits when used individually will be avoided. The former female will notice no vaginal bleeding; breast tenderness, if it occurs, will be transitory; and there will be no hirsutism. The former male will not be distressed with breast development, nor will changes in vocal pitch be noted. Regardless of how long the therapy is maintained, the problem of protein wastage in unopposed estrogen therapy will always be satisfactorily counterbalanced by the protein storage tendencies of the testosterone component of the combined therapy technique.

There is tremendous practical value in having one basic medication for all members of the "neutral gender." The pharmaceutical houses would be immeasurably aided, if a standardized steroid combination could be established and an all-gender steroid maintenance dosage delineated. Simplification of basic medication would also be a boon for the practicing physician. The margin for error in current therapy is tremendous. The market is flooded with innumerable steroid products which, when absorbed, vary greatly in strength. Even a physician experienced in steroid replacement techniques may easily err regarding the dosage schedule and functional strength of the product. The greatest present need from a therapeutic viewpoint is a meeting of the minds of both the pharmaceutical producers and the clinical and laboratory investigators, so that the clutter of hormones in the present-day market may be cleared up.

*Schedule*

Finally, for major consideration by all physicians is the unresolved question of when to initiate supportive therapy in the aging. If one acknowledges the existence of a third sex and gives credence to the reports of fortunate results with steroid supportive therapy, there remains the problem of the regeneration of debilitated individuals. Why do we have to wait until the major physical and mental disabilities of aging are well advanced, before offering assistance? Why not offset the need for a major reclamation project? Our present investigative efforts are primarily directed toward avoiding the onset of the various senile disabilities. It is a shame to allow senility its crippling influence on the members of the third sex, when the retrogressive changes of body and mind can be easily avoided or delayed in onset for years by an earlier exhibition of replacement therapy.

Perhaps the present investigative concentration on a "puberty to grave" type of steroidal support will pay future dividends. Members of the "neutral gender" who were formerly females are treated as soon as menopausal symptoms develop, and therapy is now maintained indefinitely. Delineation of the climac-

teric in the male presents much more of a problem than that in the female. However, as we concentrate more on the psychosomatic evaluation of the male climacteric, the third-sex changes become easier to define, and males are more easily diagnosed as early "neutral gender" patients. Consequently, substitution therapy is being initiated significantly earlier in many former males who previously would have had to undergo serious senile retrogressive changes before supportive efforts would be launched.

*Public health problem*

Limited individual investigative effort is not the final answer in evaluating the "puberty to grave" concept of steroid support. The fundamental necessity at present writing is a major public health project. Individuals and family units should be started on steroid supportive regimens as soon as the first evidence of the "neutral gender" is apparent. Adequately controlled conditions of maintenance and support are vital, involving another decade or two of investigation before final results are available.

One of the greatest public health problems of the present and future is the rapid increase in our aging population. If we can avoid the physical and mental degenerative changes associated with senility, or at least prevent their appearance for many years beyond present expectancy, a major contribution will have been made, not only to the treated individuals but to the economy and potential manpower supply of our country. There is not the slightest evidence to suggest—nor has any claim been made—that sex steroid support increases the longevity of the aging individual by one single day. There is no longer any question, however, as to its beneficial effects, if the steroids are administered under adequate control, and sufficiently early in the degenerative process of aging to avoid the obviously irreversible physical or mental changes of advanced senility.

## SUMMARY

Years of clinical observation and recent laboratory evidence support the thesis of the existence of a third sex. The rapid multiplication of this "neutral gender" is one of the most pressing public health problems of our present and future. Adequately controlled sex steroid support will significantly reclaim aged individuals so that they may lead a personally more satisfactory and clinically more adequate life. Of vital concern is the present effort to establish successful "puberty to grave" sex steroid support, and thus avoid significant expansion in the membership of the "neutral gender."

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# CANCER OF THE BREAST

## A Preliminary Report on a New Approach to the Problem*

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Cancer of the breast should be curable if we could treat this disease while it is still localized to the breast. That, we know, is not always possible. We are now going through the phase in which observers in certain clinics, such as McWhirter of Edinburgh, advocate a lesser operation plus radiation therapy, as contrasted to the more radical procedures suggested and practiced by Urban in New York and Wangensteen of the University of Minnesota. So, the pendulum swings from one side to the other.

During the past twenty-four years in the University of California School of Medicine, we have seen or treated 1,317 patients with carcinomas of the breast, which were classified as Stage I, II, or III lesions. Our cure rate is about the same as that reported from other large clinics. We are particularly disturbed that we are not able to cure all so-called Stage I patients, that is, those who seemingly have a localized disease without evidence of spread to the axillary lymph nodes; yet 20 per cent of this group fail to survive five years or longer without recurrence. We are all familiar with the very late recurrence. In our own experience the longest interval before recurrence was twenty-seven years after a radical mastectomy. Moreover, the patient concerned survived for more than five years after the local resection of the recurrence. In such instances, we must raise the question: Where have these malignant cells been during the long period from the time of the original operation to the time of recurrence? It is this group of cases, in which we are dealing not with an active metastatic lesion but rather with single floating cells, that we are attempting to control by the method outlined later in this paper.

### METHODS AND RESULTS

*Local excision, with or without roentgen-ray therapy.* In our series there were 19 patients who for one reason or another had simply a local excision of the tumor; some of them had subsequent radiation therapy. The ages of the group ranged from 30 to 77 years. One of these women was 30 years of age and five months pregnant at the time she was treated. Owing to the location of the breast tumor in the upper inner quadrant, the patient's age, and the pregnancy, only a local excision was performed, since it was felt that any operative procedure was practically futile. No further definitive therapy was undertaken. The patient has been followed yearly since the time of the operation in 1929. In 1954, twenty-five years later, she is still perfectly well and has reared three children.

* Presented at the Annual Meeting of the American Geriatrics Society, San Francisco, California, June 17–19, 1954.

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If we consider those who died from intercurrent causes without evidence of carcinoma and those who are still alive, our statistics show that 74 per cent of the 19 patients who had local excision, with or without radiation therapy, were apparently cured of the disease by simple, local excision of the tumor. It should be emphasized that we do not advise this as a routine procedure. Each of these cases presented an individual problem, and in each instance there was some reason why we decided against a more extensive operation.

*Radioactive phosphorus* ($P^{32}$). Because of the fact that we were not curing a considerable number of so-called Stage III cancers, we became interested in the effect of radioactive phosphorus ($P^{32}$) on these tumors. We set up a policy of treating a group of patients with Stage III carcinomas of the breast, on a purely experimental basis, by a combination of surgical and radiological procedures.

That $P^{32}$ can be concentrated by human breast cancer has been shown by many investigators. We have developed a method for preoperative diagnosis of this lesion, which is based on the differential concentration of $P^{32}$ in adenocarcinoma of the breast. Frequently the differential concentration is as high as 10 to 1. Despite this fact, however, most efforts to eradicate or to arrest metastatic carcinoma by means of intravenous administration of $P^{32}$ have led only to palliation of symptoms. When a metastatic lesion is relatively large, its differential concentration of $P^{32}$ is still not such that a cancerocidal dose of radiation can be delivered to the tumor without damage to normal tissue. However, if one were dealing, not with full-fledged metastatic lesions but with single floating tumor cells or microscopic foci of metastases, the situation might be quite different. This possibility led us to consider the use of $P^{32}$ in breast cancer as an immediate postoperative procedure, in conjunction with local intensive roentgen-ray irradiation of the primary drainage area.

*Postoperative $P^{32}$ and roentgen-ray therapy.* In 1944 we decided, as an experimental program, to treat Stage IV, and a few selected cases of Stage II and III cancers of the breast with large doses of $P^{32}$ administered intravenously postoperatively in addition to local roentgen-ray irradiation. In 1945 and 1946, 8 patients in Stage II and Stage III were treated by this method. Five of this group are alive and well at the present time (1954).

In 1947 the use of $P^{32}$ was suspended because of concern regarding possible late hematologic effects from internal radiation. We had observed that all the patients so treated had early transient depression of hematopoiesis. Over the next four years, periodic blood counts were made on these patients, and no untoward late effects on hematopoiesis developed. We therefore concluded that the procedure was safe from the hematologic point of view, and in 1951 a new, enlarged program for $P^{32}$ therapy was established.

Until September 1953, only patients with lesions classified as Stage II and III were included in this project. Since September 1953, Stage I lesions have also been treated in this manner.

The *first dose of $P^{32}$* is administered during the surgical procedure, as soon as the definitive diagnosis is made on the operating table; roentgen-ray therapy is started between the eighth and twelfth day postoperatively. $P^{32}$ treatment

consists of intravenous administration of from 20 to 30 microcuries per kilogram of body weight, two or three times a week, until the bone-compartment daily dose reaches a level of 15 to 20 gram r per gram. This dosage level is usually reached in from fourteen to twenty days and is maintained by additional doses for another ten to twelve days. The cumulative dose is calculated to be around 600 gram r per gram in the bone compartment, and around 75 gram r in the soft-tissue compartment.

The simultaneous *roentgen-ray treatment* consists of irradiation of the axilla and the supraclavicular areas up to a tissue dose of 4,000 r delivered in thirty-five days, and a 3,000 to 3,500 r tissue dose in thirty-five days to the mediastinum. In Stage I patients, roentgen-ray treatment is limited to the mediastinum and $P^{32}$ is given intravenously. The reason for the roentgen dosage in the 4000 r range is that the highest radiation voltage available to us at present is 400 KV.

Since July 1951, we have treated a total of 81 patients by operation and combined $P^{32}$ and roentgen-ray irradiation. Of this group, 6 have expired. In every patient so treated we have observed temporary marked depression of all the blood elements. Within four weeks after conclusion of treatment, however, hematopoiesis has improved. In only a few instances did supportive therapy seem advisable. These patients received transfusions, and in most cases thyroid medication was given. No other untoward effects were observed. So far, in none of the patients (even if treated back in 1944) has there been any marked bone marrow depression, and in none of them has aplastic anemia developed.

Obviously, it would be altogether premature to draw conclusions at this time with respect to the efficiency of this method of treatment. We do not expect that it will cure 100 per cent of breast carcinomas. We do expect, however, that survival rates will be improved, not only in terms of five years but in terms of ten years. It is realized that many other procedures have been advocated for the treatment of breast carcinoma, with similar hopes. Whether our method will be one more to fall into oblivion, or whether it will prove to be another step toward a successful attack on breast carcinoma, only thorough investigation and an adequate period of observation and follow-up can determine. It is our hope, therefore, that other centers will undertake to investigate the method in order to expand clinical experience more rapidly and with as large a group of patients as possible.

## SUMMARY

The use of $P^{32}$ in conjunction with surgery and local intensive roentgen-ray irradiation in the treatment of cancer of the breast is reported. Five of 8 patients treated by this method in 1945–1946 and 75 of 81 so treated since July 1951 are alive and well. Although definite conclusions cannot yet be drawn, it is hoped that this method may prove to be one further step toward a successful attack on carcinoma of the breast.

# HEADACHE: DIAGNOSIS AND TREATMENT

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It has been estimated that headache is a complaint in more than half of the patients who seek advice or attention from a physician.

It is a symptom which may be associated with a variety of clinical conditions, whether the underlying disorder be anatomic, physiologic or psychologic. Furthermore, pain always has a strong psychologic connotation and, when it is related to the head, is likely to have special meaning to the patient. Hence the clinician dealing with patients with this symptom must consider two aspects of the problem—the physiologic and the psychologic. In most instances, both are important in the diagnosis and treatment of headache.

## CLASSIFICATION

In order to deal with the problems created by headache one must start with a scheme of classification which is based on the underlying physiologic mechanisms as well as the clinical entities with which the symptom is associated.

The following suggested classification, although admittedly tentative and incomplete, allows a rational plan of diagnosis and treatment:

### 1. Migraine headache

*Cause unknown*

Presumptive Causes
1. Psychogenic
2. Endocrine
3. Hereditary
4. Allergic
5. Combinations thereof

*Mechanism*

1. Vascular
   Pre-headache—vasoconstriction
   Headache—vasodilatation, primarily of external carotid
   a. vessels dilate
   b. vessels thicken and become edematous

2. Muscular
   Muscle spasm of head and neck

*Character*

Prodromata
Gastric
Psychologic
Visual
Hemicrania—spreading
Throbbing—changing to steady ache

*Associated Symptoms*

Nausea and vomiting
Photophobia
Irritability

(Migraine variants include a group of headaches which have minor symptomatic variations from migraine. Among the descriptive names used to cover all of these variants are histamine headache, sphenopalatine neuralgia, faciocephalalgia, nasociliary neuralgia, and atypical facial neuralgia.)

### 2. Tension headache

| | |
|---|---|
| *Cause* | Psychogenic—constant or periodic emotional stress |
| *Mechanism* | 1. Vascular—vasodilatation of cranial arteries<br>2. Muscular—spasm of skeletal muscles of head and upper cervical region |
| *Character* | Bilateral—occipital or frontal<br>Variable—throbbing, dull, pressing<br>Frequency and duration—variable, but many daily or constant |
| *Associated symptoms* | Various—including anxiety, nausea and fatigue |

### 3. Headaches associated with intracranial disorders

| | Mechanism | Character |
|---|---|---|
| *Tumor* | Traction—local or distant, upon pain-sensitive structures within cranial cavity | Usually dull—deep ache, nonthrobbing, intermittent, aggravated by an increase in intravascular pressure |
| *Abscess* | ↓ | ↓ |
| *Hemorrhage* | | |
| 1. Extradural | | |
| 2. Subdural | | |
| 3. Intracerebral | | |
| 4. Subarachnoid | Irritation and traction | Intense, deep ache with nuchal rigidity |
| *Infections* | Irritation | ↓ |
| *Lumbar puncture* | Leakage of fluid through puncture wound in arachnoid and dura; probably dilatation of intracranial blood vessels and psychogenic elaboration | Intensity varies—generalized; relieved by recumbency and aggravated by erect position |

### 4. Headache associated with systemic disorders

| | Mechanism | Character |
|---|---|---|
| *Hypertension** | Dilatation—internal and external carotid arteries? | Throbbing; frequently present in the morning upon awakening; variable as to location and character |
| *Allergy* | Dilatation—internal and external carotid arteries | Periodic, occurring when patient has been in contact with offending allergens; variable as to location and character |
| *Fever* | Dilatation—internal and external carotid arteries | Variable in intensity and character; frequently deep, dull ache; may be localized or generalized; aggravated by anything that raises intravascular pressure |

* Malignant hypertension—cerebral edema.

| | | Mechanism | Character |
|---|---|---|---|
| *Endocrine* | Unknown | | Variable in intensity and character; frequently deep, dull ache; may be localized or generalized. |
| *Metabolic* | Unknown | | ↓ |

**5. Headaches associated with extracranial disorders**

| | Cause | Mechanism | Accessory mechanism | Character |
|---|---|---|---|---|
| *Muscular* | Tension; myositis local muscle injury | Spasm of skeletal muscles of head and neck | Spasm of skeletal muscles of head and neck | Deep, dull ache of neck muscles, suboccipital, frontal and other scalp muscles; movements of head and neck may be limited |
| *Osseous* | Osteoarthritis; prolapsed intervertebral disc; bone tumors (including metastatic); fracture or subluxation of cervical vertebrae | Direct neural stimulation of upper cervical and fifth cranial nerve (frequently maxillary division) | | Neuralgic (sharp stabbing), in neck muscles; movements of head and neck may be limited |
| *Nasal and paranasal* | Inflammation and engorgement of turbinates, ostia, naso-frontal ducts, superior nasal spaces | Direct neural stimulation of fifth cranial nerve (frequently maxillary division) | | Neuralgic (sharp stabbing), constant aching, usually localized in region of involved structures; intensified by increasing venous pressure |
| *Aural* | Noxious stimuli, including infection arising from the ear | | | Neuralgic (sharp stabbing), usually localized in region of involved structures; may be throbbing in otitis media |
| *Oral* | Noxious stimuli, including infection arising from the teeth | | | Paroxysmal stabbing or dull aching |
| *Ocular* | Refractive error; ocular imbalance; intraocular disease | ?Reflex stimulation; increased intraocular pressure; traction on extraocular muscles—iris | | Frequently related to use of eyes; localized to orbital, periorbital and frontal regions; aching sensation |

**6. Headaches associated with cranial trauma**

| | *Acute* | *Chronic* |
|---|---|---|
| Cause | Concussion. Contusion from laceration. Hematoma.* | Direct and indirect sources. |
| Mechanism | Foreign body reaction. Vasodilatation of cranial arteries and traction on blood vessels. Injury to nerves. | Vasodilatation of cranial arteries and traction on blood vessels. Psychologic reaction to injury. Sustained contraction of skeletal muscles of head and neck. Injury to nerves. |
| Character | Variable in character, location and intensity. Frequently widespread and intense. | No special characteristics. Variable in character, location and intensity (usually referred to part of head patient thinks was injured). May occur alone or associated with any or all of the symptoms of post-traumatic syndrome. |

**7. Psychogenic headache**

| | *Conversion* | *Tension* |
|---|---|---|
| Cause | Use of a symptom to solve a psychologic conflict, *i.e.*, bodily symptoms develop in response to emotional conflict | *See* specific syndrome |
| Mechanism | Unknown; cannot be explained on basis of any known physiologic mechanism; no experimental evidence | |
| Character | Variable; may imitate any type of headache, including migraine and those due to neoplasm | |

## DIAGNOSIS

It is well known, but often forgotten, that a careful history is usually the physician's most valuable diagnostic aid (1). This is especially true in any in-investigation of headache. The patient should be allowed to describe freely his symptoms and related factors. Leading or direct questions should be postponed until later in the investigation. In taking a detailed history the physician not only gains information but establishes rapport with the patient. Elicitation of the following information is especially important.

1. Onset of the headache should be carefully considered. A record should be

* See intracranial disorders.

made of the circumstances under which the first headache occurred and factors predisposing to subsequent attacks, such as physical and psychic trauma, infections and inflammations, allergies or cyclic events.

2. The time of day most favorable to a particular headache may be helpful in diagnosis; for example, persons with histamine headaches are characteristically awakened by the pain and move about with great abandon, whereas those with migraine often awaken with a headache but movement aggravates the pain. Other types of headaches may also be nocturnal, even the psychogenic type. Hypertensive and sinus headaches may occur in the early morning after the patient has awakened, but ocular headaches are apt to occur later in the day.

3. The character of the pain is at times helpful. However, it is as often misleading. Pain described in a wealth of metaphor and by a lavish use of superlatives is not necessarily the psychogenic type, which may in turn simulate any kind of organic pain. Throbbing headaches, however, indicate a vascular mechanism, even though the etiology be psychogenic. The headache of migraine is characteristically throbbing at the onset but later becomes constant.

4. The location of the pain is also of aid in diagnosis, but it may be misleading. A well localized pain often indicates a local pathologic condition, such as frontal sinusitis or cerebellar tumor, but it may also be due to distant foci of irritation. In general, headaches anterior to the ear are due to direct or indirect stimulation of supratentorial structures, whereas those below or behind the ear are due to subtentorial irritation. The latter may be due to cerebellar tumor, cervical lesions, muscle spasm or emotional tension, whereas the former may be due to any cranial or extracranial disorder.

5. The severity of the headache is entirely nonspecific. Duration and frequency are of little value diagnostically. Chronic psychogenic headache may be more severe than that due to an early tumor.

6. The effects of posture and motion are occasionally of differential value; for example, movement of the head and neck does not usually aggravate an emotional headache, whereas the opposite is true in headache due to cervical disorders, sinusitis, or migraine.

7. Certain associated signs and symptoms, such as nausea and vomiting, are nonspecific and may occur with any headache or even on a purely emotional basis. Visual disturbances, such as diplopia, homonymous hemianopia, dilated pupil and ptosis may occur with migraine headaches. However, if the visual defect outlasts the headache, it is likely that there is an organic brain lesion.

Vertigo may be a premonitory sign of a migraine headache, but it may also be associated with headaches which are post-traumatic, or due to brain tumor or emotional tension.

## EXAMINATION

Examination should always include inspection, palpation, percussion and auscultation of the head (1), if only to develop rapport with the patient. Although these measures infrequently reveal any pertinent lesion, this approach at once develops considerable confidence in the physician.

A complete neurologic examination is indicated in every case, with emphasis upon the ophthalmologic examination, which should include evaluation of the optic fundus, lens, media, and the intraocular and extraocular motility. Tumor, hematoma and aneurysm must always be excluded when headache is a prominent symptom. A search for sinus tenderness, and observation of the nasal airways is routine. The muscles of the scalp and neck should be examined for muscle spasm, tenderness and nodules. Cervical motility and sensitivity should be evaluated.

Certain laboratory procedures may be useful, but it has been our experience that the findings are usually normal. In our routine studies we include urinalysis, a complete blood count, a serologic test, roentgenography of the head and neck, electroencephalography and ophthalmologic evaluation. The roentgen and ophthalmologic examinations have been of greatest value. (It should be noted that peripheral fields were explored with minimal size test objects, *i.e.*, 2/330 and 1/330 white; and the inner and central fields with 1/2000 white.)

Allergic studies, ear, nose and throat examination, metabolic determinations and examination of the spinal fluid contribute little of significance in the average case.

Probably the most helpful procedure is a careful personality study, without which no examination is complete. This usually provides considerable information which can be useful in the management of the case and often discloses significant causal factors. Furthermore, such a personality evaluation is in reality a therapeutic, as well as a diagnostic measure. A word of caution, however, must be added. It does not follow that because a person harbors personality problems, these problems are necessarily the sole, or even the predominant cause of the headache. Many persons with similar personality disorders do not have headaches or, in fact, any recognizable symptom-complex.

An outstanding example is the often quoted statement that headaches due to sustained muscle contraction in the neck and scalp are usually psychogenic. This is an unfortunate generalization, as local cervical pathologic conditions or even generalized infections may be the underlying factor, often requiring careful local and general examination. Too often these patients are subjected to prolonged psychotherapy, without benefit of any kind.

## HEADACHE ENTITIES

The great majority of headaches fall into three groups—migraine, tension or post-traumatic. However, in the older age-group other types of headache may also appear, particularly those associated with hypertension, osteoarthritis and temporal arteritis.

In the following sections particular emphasis will be laid upon all the types of headache previously mentioned. Several thousand such patients have been studied and treated during the past ten years.

### *Migraine*

Migraine is a syndrome in which the outstanding feature is periodic unilateral headache, usually associated with gastrointestinal symptoms and often preceded

by visual or psychologic disturbances. There is frequently a history of similar headaches in the parents or other members of the family.

The specific underlying causes of migraine are unknown. The mechanism of the symptoms is a matter that is more clearly understood, and is considered to be on a vascular basis (2, 3). An initial vasoconstriction of the cerebral arteries produces visual, and possibly other pre-headache phenomena, prior to the onset of the headache. This prodromal period is then followed by dilatation and distention of cranial arteries, primarily in the distribution of the external carotid artery. This arterial dilatation, with the accompanying increased amplitude of pulsation, is presumed to cause the headache. Persistent dilatation results in rigid, pipelike vessels. The pain at this stage is a steady ache replacing the earlier throbbing, pulsating pain owing to dilated vessels. During or following this, there is a "muscle-contraction pain." This spasm is a reaction to the migraine pain and may outlast it. The headache itself arises from the stimulation of nerve endings which lie in or near the walls of the intracranial arteries, whereas the muscle pain is a result of direct stimulation of nerve endings in the muscle.

*Tension headache*

Tension headache occurs in relation to constant or periodic emotional conflict, of which the patients are usually partially aware (4). These headaches have no prodromata, are usually bilateral, occipital or frontal, and may be accompanied by a variety of associated signs including anxiety, nausea, and vomiting. Frequency and duration are variable.

In tension headache, muscular or vascular mechanisms may act independently or concomitantly. With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia, which could be a contributory or primary factor in the induction of pain. It has also been hypothesized that excessive concentration of potassium in muscle, due to ischemia or sustained contraction, stimulates the chemoreceptors in the tissues. Another factor responsible for the head pain may be a central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

Under stress, a discharge may occur in the autonomic nervous system, with resultant changes in the cranial blood vessels. The end-organs for pain surrounding these blood vessels are stimulated and create nerve impulses which pass along the afferent pathways to the central nervous system.

*Post-traumatic headache*

One of the first and most frequent sequelae to injury of the head is post-traumatic headache. The acute type is rarely a problem because, when first seen, the patients are comatose and later, under correct treatment, have little or no headache. In the chronic group, a headache persisting longer than two months following trauma is a more difficult problem for the physician to treat. Such headaches may appear singularly or in association with such symptoms

as dizziness, difficulty in concentration or nervousness—the so-called post-traumatic syndrome. This occurs in approximately 60 per cent of patients who have had head injuries (5).

In studying a large series of patients following head injury, the incidence of prolonged headaches was high among patients 1) with neurotic symptoms prior to injury, 2) with symptoms of marked, immediate emotional reactions to the injury, and 3) with complicating environmental factors which might be presumed to cause unusual emotional stress.

The physiologic mechanisms which are presumably involved in the production of post-traumatic headaches are distention of cranial blood vessels, sustained contraction of the skeletal muscles of the head and neck, and scarring of the extracranial soft tissues.

In a small number of patients with post-traumatic headache the cause is subdural or subarachnoid bleeding, adhesions involving the pia-arachnoid, injury to the cranial nerves, or injury to the superficial or deep structures of the neck.

In most patients with post-traumatic headache, the pain has no special characteristic. Although many refer to it as a pressure or band-like sensation, others describe a recurrent periodic throbbing pain. The headache is usually referred to the side or part of the head which the patient associates with the injury. It may be regular or intermittent, generalized (bitemporal or bifrontal) or unilateral, and may vary in frequency and duration. It may be precipitated or aggravated by emotional stress, change in posture, fatigue or effort, but may appear without any such precipitating factors. Such post-traumatic headaches resemble tension headaches.

*Hypertensive headaches*

Severe headache is often a major complaint of most patients with essential hypertension at one time or another. The headache of arterial hypertension is usually a dull, throbbing, deep ache. It is aggravated by strain, stooping and emotional tension. This headache may be generalized or confined to the front or back of the head. Although usually bilateral, it may resemble migraine in its periodicity and in being confined to the one side of the head. It often appears upon awakening and may improve as the patient moves about. Nausea and vomiting are infrequently noted.

Another variety of headache occurring with hypertension is a suboccipital tightness and rigidity, which may encircle the head. This is due to muscle spasm and is similar in mechanism to tension headache.

The pathogenesis of headache in essential hypertension is somewhat obscure. The increase in blood pressure is not commensurate with the degree of headache. The headache may be present when the blood pressure is low, as well as when it is high. It is postulated that variations in the contractile state of the cranial arteries are the cause of the pain and that the elevated blood pressure is only an accessory factor. After administering ergotamine tartrate the headache usually disappears, which would indicate that the mechanism may be similar to that of migraine.

This headache is not due to increased intracranial pressure, because intra-

cranial pressure is normal, and elevating it experimentally will not produce the head pain. There is also no relationship to impairment of renal function. It is of interest that the headache does disappear after sympathectomy, even though the operation may not appreciably lower the blood pressure. However, when the blood pressure is lowered by therapeutic measures such as sodium restriction, antipressor drugs or sympathectomy, the headache usually disappears.

When hypertension develops in association with the menopause, headache is often a common complaint, but such hypertension is usually transient. Headaches are often encountered in cases of essential hypertension associated with arteriosclerosis, and they are most difficult to treat.

Malignant hypertension is characterized by Fishberg (6) as a clinical picture manifesting itself by increased intracranial pressure, headache, vomiting, papilledema, renal insufficiency, and often stupor and convulsions. The headache in these instances is thought to be a result of edema of the brain. The edema creates traction upon, and displacement of pain-sensitive structures. The mechanism, therefore, is similar to that in cases of brain tumor. These headaches are often intense and continuous.

*Temporal arteritis*

Temporal arteritis may be acute or subacute, affects women more than men, and is more common in later life (55 to 80 years). Horton, Magath and Brown (7) first described the clinical entity of temporal arteritis in 1932. The term may be misleading, as the lesion is now considered by some to be a part of generalized arteritis of unknown etiology. The pain is usually constant and is most often located in the temporal region, although the occipital and parietal areas may be involved. The pain is severe and is aggravated by straining, coughing and chewing. The patient often finds it extremely painful to chew, and is usually in a state of fatigue, fever, weakness, profuse sweats and leukocytosis. His general appearance is that of a person who is acutely ill. Manifestations accompanying the head pain often include photophobia, ptosis, diplopia and partial visual loss. The retinal arteries may reveal arteriosclerosis, hemorrhage or exudate. These changes may be associated with loss of vision.

Upon examination the affected blood vessels are often hard, nodular and sensitive. Sections of the artery which have been removed from these patients show a tortuous condition, with thickening of the walls resulting in a decreased lumen; in some cases a thrombosis has been found. The cellular infiltrate is composed mainly of mononuclear cells and fibroblasts, with scattered eosinophils and giant cells. This is suggestive of a granulomatous process. It seems to differ from periarteritis nodosa clinically and pathologically. In the latter the cellular infiltrate is composed mainly of polymorphonuclear leukocytes. Occasionally, however, a case of temporal arteritis may exist as a manifestation of widespread arteritis.

*Cervical osteoarthritis*

In the presence of advanced osteoarthritis, persistent contraction of the suboccipital muscles may develop and give rise to pain or dysesthesia in the neck

or scalp. The headache in this condition is usually located in the occipital and suboccipital areas, may involve the parietal or frontal region, and radiates down the back of the neck into the shoulders. It may be unilateral, but in most cases it is bilateral. The pain varies in intensity and may be described as a feeling of tightness or a deep ache. It is usually constant and is increased by movement of the head. The onset of the pain may be either sudden or gradual. The musculature of the suboccipital area is very tight during the acute phase of cervical arthritis and may often be in a state of spasm. The patient may hold his head in the position that is most comfortable to him. Examination reveals muscular contraction of nodular areas and points of tenderness.

Although headaches associated with osteoarthritis differ from other headaches in their basic etiology, the mechanism which produces the pain is similar. Associated with these muscle spasms may be ischemia, excessive potassium concentration and central spread of the excitatory effect.

Furthermore, under such stress a discharge may occur in the autonomic nervous system with resultant changes in the cranial blood vessels. The end-organs for pain surrounding these blood vessels are stimulated and create nerve impulses which pass along the afferent pathways to the central nervous system. The result is a headache with both vascular and muscle-spasm components.

## TREATMENT

The object of treatment is twofold—to relieve the underlying cause and prevent subsequent attacks, and to alleviate the pain of an immediate attack. The four main methods available for the treatment of headache are pharmacotherapy, psychotherapy, physiotherapy and surgery. The first two are used predominantly.

This paper is limited to a consideration of some general principles in headache therapy, with special reference to the types of headache previously discussed.

### *General considerations*

1. *Pharmacotherapy.* Although in some cases the use of drugs may not solve the basic therapeutic problem, they are of considerable value in the treatment of headache.

Pharmacologic treatment involves an attempt: 1) to raise the pain threshold, 2) to interrupt the mechanism which produces the pain, or 3) to reduce the emotional tension and anxiety associated with the pain. However, the efficiency of any drug does not depend upon its pharmacologic action alone. The importance of dosage, timing, mode of administration and toleration by the patient can not be stressed sufficiently. Furthermore, such efficiency greatly depends upon the patient-physician relationship, which includes among other things the length and frequency of interviews with the patient. Our experience indicates that patients' reactions to drugs not only may depend upon the underlying disorder which causes the headache, but also upon the degree of incapacity, the constitutional make-up and age of the patient, the duration of symptoms, and the psychologic status. What the medication symbolizes to the

patient is also a contributory factor in treatment. Is the taking of medication a sign to the patient of weakness, of receiving omnipotent mystical power, or of love and affection? All these factors must be given serious consideration in the clinical usage of drugs in treatment of headache.

In evaluating the subjective symptoms of head pain, there is such a tremendous psychologic factor that great care must be used in reporting success with any type of treatment. Investigating the literature and some of our own work, we note that the good results obtained by the primary investigators are frequently not duplicated on subsequent tests.

2. *Psychotherapy.* The importance of psychologic factors in the etiology of many cases of chronic headache is widely recognized. To the patient, a symptom related to the head is frequently associated with profound anxiety, due not only to the underlying etiologic emotional conflicts but to the threat of the symptom itself. Headache also represents to the patient a fear of loss of the mind, disorder of the brain or loss of intellectual capacity.

It is assumed that psychogenic factors produce symptoms in two different ways. One way is by means of a conversion, in which an emotional conflict is converted into a physical dysfunction. Such conversion phenomena are often understood in terms of their symbolic meanings. To understand the specific meaning of such a symptom one needs to be familiar with some general principles of dynamic psychotherapy in addition to specific information about the person with the symptom.

Psychogenic disturbances may also be directly expressed as alterations of specific physiologic functions, and are often due to an existing emotional feeling or tension state. Very often these physiologic alterations are not the result of conversion, as seen in cases of conversion hysteria in which psychic "energy" derived from the repression is "converted" into a physical symptom or sign. In some patients, however, both the foregoing mechanisms may be observed simultaneously.

Psychotherapy is directed toward relieving the emotional tension and stress which is the precipitating factor in the attack of tension headache. The most important single factor in the psychotherapeutic process is the emotional relationship of the patient to the physician (8). This relationship dominates the treatment, despite the fact that it may be explicitly discussed only rarely, or not at all. In complete psychoanalysis, this relationship is clearly recognized by the therapist.

In emphasizing the importance of the physician-patient relationship, one must not overlook the importance of other aspects of psychotherapeutic procedures as, for example, environmental manipulation and the ventilation of wholly or partly unconscious emotional conflicts by the patient.

In environmental management one has to recognize and deal with the patient's capacity to handle his work, recreation, and family and social life. The physician should strive to correct the patient's program so that work, play and rest are balanced. In some cases a sustained hobby is of value in securing relief from tension and daily stress. Concerning any changes in the patient's way of life, it

is important that the doctor assist the patient in making his own decisions, rather than make such decisions for him.

Often it is more practical and more satisfactory to have the patient adjust to his environment rather than alter it. This is accomplished by having the patient discuss his problems thoroughly, with the aim of gaining greater understanding of his emotional difficulties. He may thus achieve freedom from needless anxiety, enabling him in turn to cope with actual stressful situations. The physician must learn to listen patiently and create trust and confidence.

Often simple explanations of the effect emotions have on bodily functions and the relationship of stress situations to development of symptoms, may give the patient insight into what happens to him during periods of stress. Reassurance, suggestion, and re-education are other technics which may help.

Such therapy is within the province and ability of the interested general practitioner. With this treatment, over-all improvement in terms of a greater capacity for life adjustment and a reduction of habit patterns which activate the physiologic mechanism causing the headache, may be anticipated. In some patients in whom reorganization of the personality is necessary to secure relief, formalized psychiatric treatment is necessary.

*Treatment of migraine*

1. *Symptomatic.* Symptomatic treatment of migraine is rendered most effective by the use of oral or rectal ergotamine tartrate and caffeine (Cafergot). Rectal Cafergot has proved empirically to be most efficacious, especially when oral medication cannot be retained (9). Apparently the rectal route has the advantage of allowing the drug to be absorbed more directly into the systemic circulation, without having to penetrate the hepatic and gastric barriers. Hence it is postulated that results are obtained more quickly and with fewer side effects by rectal than by oral administration. This requires further investigation.

For each attack the average initial oral dose of Cafergot is two tablets (each tablet contains 1 mg. of ergotamine tartrate and 100 mg. of caffeine) followed by one tablet at half-hour intervals (up to a total of six tablets) until the necessary effect is produced. However, the minimum effective dose must be determined individually for each patient. The average rectal dose is one suppository (2 mg. of ergotamine tartrate and 100 mg. of caffeine) every half hour, using a total of three suppositories if necessary.

The importance of administering the medication early in the course of an attack, as well as in adequate doses, cannot be overestimated. Many failures in therapy are caused by an inadequate dose given too late. The optimal time of administration is in the prodromal period, or immediately after onset of the headache.

The side effects of ergotamine tartrate are variable and may include nausea, vomiting, tingling of hands and feet, pains in the neck, thigh and abdomen, and substernal oppression. In some cases, a careful history reveals that these symptoms are associated with the migraine and are not due to the medication. Muscle spasm may occur in the extremities and can be ameliorated by massage or exercise. There may also be perivascular pain. Nausea and vomiting and in-

testinal spasm may be relieved by using atropine sulphate, 0.65 mg. (1/100 gr.), before or during the administration of ergotamine.

In general, none of these symptoms, if transient, contraindicates the use of ergotamine tartrate in the absence of infection, pregnancy, or organic disorders of the heart, liver, or peripheral vascular system. If persistent paresthesias, substernal oppression or pain in the abdomen or extremities occur, the drug should be discontinued.

In some patients ergotamine tartrate is poorly tolerated and the use of dihydroergotamine methanesulfonate (D.H.E.-45) is indicated. Dihydrogenation of ergot reduces the vasoconstrictive action. In order to produce an equivalent therapeutic effect, dihydroergotamine must be given in doses twice as great as those of ergotamine tartrate. It can only be administered parenterally and, like ergotamine, must be given as early as possible in the attack. The usual dose is 1 mg. intravenously or subcutaneously, to be repeated in an hour if necessary. Efforts to abort the attack in the prodromal phase by means of vasodilatation with such drugs as amyl nitrite, nicotinic acid, oxygen and $\beta$-methylacetylcholine (Mecholyl) have been uniformly unsuccessful.

Analgesics and sedatives are sometimes indicated if the headache has been present long enough for edema to take place and the vessels to become firm and tortuous. In these cases codeine phosphate (60 mg.), with or without sodium Amytal (0.2 Gm.) or Seconal (0.1 Gm.), is indicated.

2. *Prophylactic.* It is well known that in most patients with migraine suitable psychotherapy may be of great value in reducing the intensity and number of attacks and may even result in their disappearance for a considerable time. The details of this type of treatment have been discussed under general considerations of psychotherapy.

Adequate relaxation, improvement in sleep and correction of any physiologic abnormalities are aids in reducing the frequency of the attacks. In a few cases there may be evidence that the precipitating mechanism is of an allergic, endocrine or "metabolic" nature, but these factors are too rare to have significant application to therapy. However, when an offending allergen is the cause, it should be removed or the patient desensitized. If the onset of migraine is associated with the menstrual period the use of progesterone or testosterone, or both, may be helpful. In some patients, premenstrually, a diet that restricts the daily intake of salt in addition to a diuretic seems to be beneficial.

Drugs such as histamine or nicotinic acid are of no value. Sedatives to reduce emotional tension are limited in their usefulness. More recently we have used reserpine and chlorpromazine hydrochloride (Thorazine) as interim treatment, but results have not been encouraging.

The periodic and often paroxysmal nature of migraine and other types of vascular headache brought forth the idea that treatment with anticonvulsants might be of value in these disorders. Of the anticonvulsant drugs, we have had experience with only Dilantin and Mesantoin. Both are hydantoinates. These are analogous to the barbiturates, being derivatives of glycolyl urea as compared with malonyl urea.

A small number of migraine sufferers respond well to Mesantoin, or Dilantin

prophylactically. This limited group consists of patients who have an aura of aphasia, paresthesia, or hemiplegia prior to the headache and an abnormal electroencephalogram. In certain other cases in which there is a family history of migraine and epilepsy and the electroencephalogram shows abnormal brain waves with spiked patterns, the use of certain anticonvulsant drugs is of value in reducing the frequency, severity and duration of the headache. Dilantin and Mesantoin are administered orally. The initial dosage is usually 0.1 Gm. two or three times daily; this is gradually increased until satisfactory control is obtained. It is best to take about a week to reach the threshold dose, although most adults can tolerate 0.3 to 0.4 Gm. daily without toxic effect.

Both hydantoinates, Dilantin and Mesantoin, may produce bizarre and unsuspected side reactions, which occasionally may limit their usefulness in therapy. Among the toxic effects of Dilantin are gastrointestinal upsets and central nervous system disturbances, including giddiness, ataxia, tremor, nystagmus, and slurring of speech. Hyperplasia of the gums is common in childhood and young adults. Skin eruptions, usually of scarlatiniform type, are occasionally seen. Precordial pain, when it occurs, may be associated with prolonged PR intervals and flattening of the T wave in the electrocardiogram. Mesantoin may affect the hemopoietic system, the particular manifestation being an increase in the number of lymphocytes and depression of the polymorphonuclear leukocytes. Hence it is necessary, when treating patients with this drug, to have blood counts made at regular intervals. Following the use of Mesantoin, cases of aplastic anemia and leukopenia have been reported. Skin rashes are encountered somewhat more frequently than with other hydantoin anticonvulsants. Fever and lymphadenopathy are also seen.

*Treatment of tension headache*

1. *Symptomatic.* Symptomatic relief from tension headache is secured by drug therapy. As in the case of psychotherapy, flexibility must be the keynote. The treatment of tension headache is nonspecific, but the purpose of therapy is to relieve tension and raise the pain threshold. This is best accomplished by use of an analgesic-sedative combination. Such a combination should act with minimal side effects, allowing the patient to maintain his environmental relationships and not be a problem because of possible addiction or the development of tolerance.

For symptomatic medication in the treatment of tension headache there are several analgesic and sedative combinations (9). One of the most effective is Fiorinal (isobutyl-allyl-barbituric acid, 50 mg.; caffeine, 40 mg.; acetylsalicylic acid, 200 mg.; and acetophenetidin, 130 mg.). Daprisal (*d*-amphetamine sulfate, 5.0 mg.; amobarbital, 32 mg.; acetylsalicylic acid, 162 mg.; and acetophenetidin, 162 mg.) is also effective in patients with tension headache. In some cases Empirin compound (acetophenetidin, aspirin and caffein) will suffice.

2. *Prophylactic.* Control of tension headaches can best be accomplished by use of psychotherapy, for this is the only method in which the patient's emotional conflicts can be resolved.

The injection of 1 per cent procaine directly into the tender areas of the neck

may eliminate the headache for several hours or a few days. The long-term use of procaine in tension headache is not consistent with the underlying mechanism causing the headache.

Sedatives such as barbitals, and analgesics afford only temporary relief. Furthermore, their side-effects curtail prolonged usage.

More recently we have used *Rauwolfia serpentina* (reserpine) in over 50 patients with tension headaches. They have now been treated for periods of two to five months, with relatively good success. Improvement was noted in two-thirds of the patients receiving an average dosage of 0.75 mg. daily. Little difficulty was encountered from side effects. However, the effectiveness of any drug in headache patients depends upon a multiplicity of factors. The result with reserpine should be considered only as preliminary and not conclusive.

*Treatment of post-traumatic headache*

In the treatment of chronic post-traumatic headache the type of therapy is similar to that in the treatment of tension headache (10). It should be emphasized that if the head pain is from such causes as subdural hematoma, or injury to deep structures or the neck, the underlying disorder must be treated.

It is considered important to accelerate convalescence in patients with head injury, whenever possible. This reduces the usual sequence of head-injury symptoms, including headache. By hurrying convalescence and making a post-traumatic patient ambulatory, his anxiety is minimized and he is reassured as to the extent of his injury. This reassurance seems essential in these cases, and is the apparent reason for the inverse correlation between bed rest and disappearance of symptoms.

Symptomatic treatment of patients is best accomplished by use of mild analgesics such as an aspirin compound, or a mild sedative combined with the analgesic. In some cases the addition of codeine to these preparations may be necessary. When the superficial scar of a head injury becomes an area of constant tenderness and aching pain, the injection of 1 per cent procaine into the tender area may temporarily eliminate the head pain. A similar result can be obtained in headaches in the occipital and subnuchal region due to muscle contraction.

For prompt and long-lasting response to therapy, an organized psychotherapeutic approach is indicated, as outlined in the general discussion on psychotherapy. Reassurance, ventilation and re-education are the ultimate goals.

The use of tranquilizers such as reserpine may be beneficial in chronic post-traumatic headache. The adjustment of dosage will vary with the patient. After a maintenance level is reached, the daily dosage range is 0.5 to 1.0 mg.

*Treatment of hypertensive headache*

In the treatment of hypertensive headaches, management of the general state of hypertension is always indicated, aiming at a decrease in the blood pressure and protection of the patient against vascular insults. The available measures for lowering the pressure include psychotherapy, rest, sodium restriction, specific antihypertensive drugs and sympathectomy.

1. *Symptomatic.* Symptomatic treatment is best conducted by use of analgesics such as aspirin or codeine combined with sedatives. Although ergotamine may prove beneficial in ameliorating the headache, its use in these patients is not advisable.

2. *Prophylactic.* Antipressor drugs used for the reduction of blood pressure include the methonium salts, Dibenamine hydrochloride, hydralazine, hydrogenated ergot alkaloids and *Rauwolfia serpentina* (reserpine).

Recently we have used reserpine in a group of over 30 patients with hypertensive headache. This drug acts as a hypotensive agent as well as a sedative. Although not a potent hypotensive drug it has proved to be effective in reducing the severity and frequency of the headache as well as producing a moderate lowering of the blood pressure. These 30 patients have been taking reserpine for a period of from two to five months and have showed no marked secondary effects. We are encouraged by the results, but more time is needed to prove the efficaciousness of this drug. The average dosage is 0.25 mg. three times daily.

Sedatives may be useful in hypertensive patients who show anxiety, excess tension and irritability. We have used Amytal, 0.75 Gm. two or three times daily, and have noted slight reduction in blood pressure and some amelioration of nervous symptoms. In a small number of patients the headaches are reduced in frequency and severity by this measure. However, it should be pointed out that these patients have usually been on a regimen of rest, dietary restriction and modified psychotherapy.

Dietary restrictions have always played a role in the treatment of hypertension. In recent years sodium restriction has been regularly used in treatment. As pointed out by Weston and his associates (11), intensive salt restriction should be instituted with care in the presence of impaired renal function.

*Surgery.* Sympathectomy as a method of combating high blood pressure is advised only after careful and objective evaluation of the problem. It is used in less than 4 per cent of cases with hypertension (6), but the results have been effective in this select group.

*Psychotherapy.* Hypertensive headaches can often be related to emotional tensions and life stress. The value of psychotherapy in these cases is considerable. Management is similar to that described for migraine and for tension headache.

Malignant hypertensive headaches are treated mainly by reduction of intracranial pressure. The methods used include slow cautious drainage of the cerebrospinal fluid, venous section, administration of hypertonic glucose, low sodium diet and sedation.

### *Treatment of temporal arteritis*

The headaches associated with temporal arteritis are often intense and it is frequently necessary to use 60-mg. doses of codeine. Procaine infiltration of the vessel wall is sometimes helpful as a temporary measure.

There is no specific treatment for temporal arteritis. ACTH and cortisone have not been effective in our experience. Excision of the involved artery will sometimes result in considerable improvement.

*Treatment of cervical osteoarthritis*

Analgesic groups of drugs combined with sedatives are helpful in controlling the pain associated with cervical arthritis. Rest in bed, local heat (either wet or dry) and massage are helpful adjuncts in therapy. The injection of 1 per cent Novocaine directly into the tender area may be of value. In some cases traction of the neck is useful in relieving muscle spasm and pain (12).

## SUMMARY

Based on a practical classification of headaches, an analysis of the diagnostic and therapeutic criteria is presented. Specific headache entities frequently seen in the older age group are discussed.

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# THE RELIEF OF TIC DOULOUREUX (TRIGEMINAL TIC) AND OTHER PAINS OF THE FIFTH CRANIAL NERVE BY INJECTION OF HOT WATER INTO THE GASSERIAN GANGLION

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Tic douloureux is a severe persistent paroxysmal neuralgia affecting the distribution of all or a part of the sensory branches of the fifth cranial nerve. It is characterized by sharp, stabbing, lightning-like pains which are referred to the tongue, lower lip, jaw and teeth, the upper lip and teeth, the malar region, the forehead and sometimes the temple. The patient's sleep may be uninterrupted during the night and the pain may disappear completely for hours, days or many months. Talking, eating, drinking, stroking the face and cold air aggravate the distress. As time passes, there is a strong tendency for the pain—which may have started in a very circumscribed area—to extend to areas adjacent to the painful spot. Frequently the entire side of the face and jaw are ultimately involved. It commonly affects those in the late years of life, but it is not unknown in childhood.

Once the disorder starts, relief can be obtained only through a temporary merciful spontaneous remission or by destruction of the involved nerve elements by operation, alcohol injection or heat. The numerous cures or reliefs claimed following the use of various agents such as vitamins, drugs, or physiotherapy do not take sufficiently into account the frequent long spontaneous remissions which are characteristic of the disorder. If an experienced observer were to be given two groups of 100 patients, each with tic douloureux, and one group were to be treated by any present medical or physiotherapeutic method, the other to be treated by placebos—over a period of ten years—there would be no difference in the degrees of relief obtained.

*Nerve-root section and alcohol injection.* Patients with tic douloureux and certain other disorders (such as cancer of the face) that affect the fifth cranial nerve or the anatomic structures that are supplied by it, have in the past been permanently relieved of pain only by cutting the sensory root between the pons and the gasserian ganglion or by actual destruction of the nerve cells of the ganglion by chemicals. Alcohol has been the most commonly employed chemical agent for destruction of the ganglion cells. On many occasions, it has seeped into the cerebrospinal fluid surrounding the ganglion and extended its effects downward to paralyze the facial, hypoglossal, acoustic and vagus nerves. Personally, this happened in my experience after injecting only 2 drops (0.2 cc.) of absolute alcohol into the ganglion. Such an unfortunate result is permanent, although the pain may not return. It is common knowledge that to obtain permanent relief the ganglion cells must be reached by the injected alcohol. This thin, anatomically

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invisible line between destruction of cells and overflow of the alcohol into the cerebrospinal space bathing the cells, has led to the almost universal abandonment of ganglion injection by the neurosurgeon in favor of safer, temporary, peripheral-branch injection or section of the sensory root by craniectomy. In a well trained brain surgeon's hands, the major operative procedure for permanent relief has been remarkably safe, as shown by Peet and Schneider (1). They reported a mortality of 1.6 per cent in 553 patients. A recent review of 119 consecutive Jefferson Hospital patients operated on by the author by the suboccipital approach showed 3 deaths (2.5 per cent). However, it is probable that most good neurosurgeons maintain their poor-risk tic patients with repeated injections into peripheral branches, rather than subject them to the hazards of the major operative procedure. This is only partially satisfactory to the patient, who frequently delays returning to the surgeon for other injections because too often these have been very painful procedures, coupled always with the unpleasant assurance that "the pain will return when the numbness wears off."

*Decompression of trigeminal root.* In the summer of 1952, I visited Dr. Bendt Broager, Neurosurgeon at Busch's Clinic in Copenhagen, and was told that Palle Taarnhøj's decompression of the trigeminal root (as had been previously reported (2) in 10 cases in 1952) had been extended to 20 cases and that the relief continued to be satisfactory. On returning to my clinic, I determined to try out the procedure. On September 29, 1952, I performed section of the dura overlying the ganglion and the superior petrosal sinus according to Taarnhøj's technic, on a 48-year old woman. The electrocoagulator was used for control of venous bleeding. Postoperatively there was a sensory loss over the tongue and corner of the mouth, exactly like that following suboccipital partial sensory-root section. The second patient was a boy of 12 years who had been observed closely for many months for fear the pain might be psychogenic, although typical of tic douloureux. The ganglion and root decompression was carried out and extended to the tentorial edge. The electrocoagulator was used over the intact dura covering the structures to stop venous bleeding before sectioning it. The fourth cranial nerve was inadvertently cut in my eagerness to be thorough. Following the procedure, there was ganglionic cell destruction as manifested by a hypalgesic area which was most marked at the corner of the mouth and other parts of the second and third branches—a pattern similar to that in the first patient. At present, two years later, both of these patients have precisely the same hypalgesic area as immediately following operation and have been completely relieved of pain.

Further experiences with Taarnhøj's operation by American surgeons, and by Taarnhøj himself, indicate a high percentage of recurrences and the usual complications of subtemporal route operations. Taarnhøj has recently reported (3) on the incidence of postoperative pain referable to the old disorder (24 per cent). In his entire group of 76 patients (33 with "atypical trigeminal neuralgia" and "facial pain"), there were 15 patients with trochlear nerve palsy and 2 with "transitory palsy of the facial nerve." Love (4) reported on 100 consecutive cases; there was a fatal result in 1, facial palsy in 16, sensory impairment in 27 and complete immediate relief in 51. This report reflects rather accurately the

impressions of others who have had experience with this method. From my personal observations, it would appear that equally good results may be obtained at far less risk by merely steaming the ganglion with the electrocoagulator applied directly over the intact overlying dura. This should decrease or even eliminate complications such as facial or ocular nerve paralysis and hemorrhage from the petrosal sinus and meningeal vessels. A dry cornea caused by petrosal nerve damage and paralysis of lacrimation could, in all probability, be avoided.

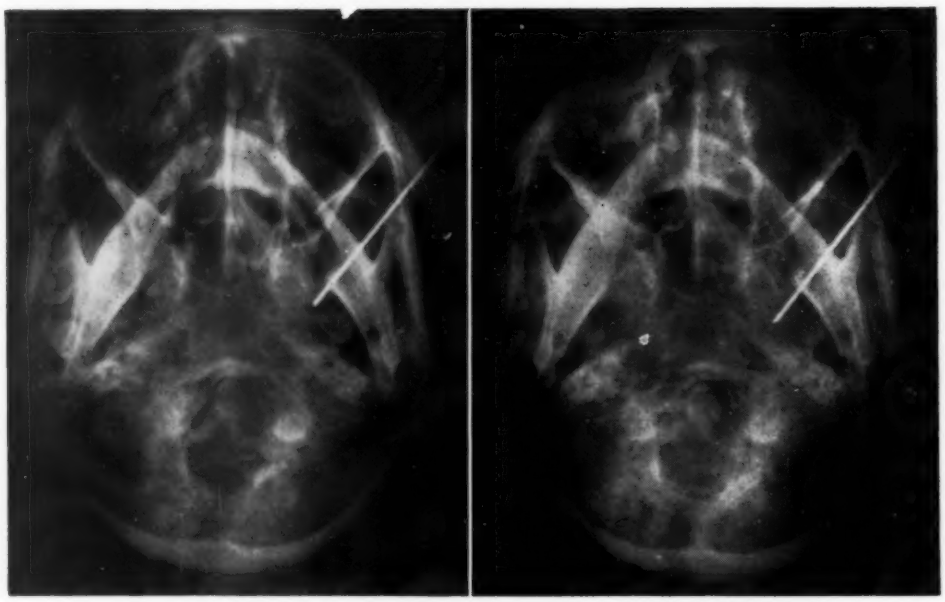
*Injection of ganglion with hot water.* It was obvious from postoperative observations on the 2 patients mentioned that both the hypalgesic area and relief of pain were due to heating the cerebrospinal fluid around the ganglion cells by coagulating the overlying dura. I reasoned that if hot cerebrospinal fluid could kill ganglion cells, then simple injection of hot water through the foramen ovale into the ganglion (even attempting to inject directly into the surrounding cerebrospinal fluid-bearing space) should achieve the same result. The first case bore out my contention. When 1 cc. of boiling water was injected into the ganglion, with or without aspirating fluid, it was remarkable how the hypalgesic pattern resembled those described in the 2 ganglion decompression cases. Subsequent successful attempts have been made to repeat this initial success. The technic has necessarily been developed by trial and error, but since the investigation has been carried through painlessly and with no major complications, the results have been well worth the effort. With further improvement, the reward would appear to exceed initial expectations.

## TECHNIC OF HOT-WATER INJECTION

The procedure is carried out in the radiographic room under light pentothal anesthesia on a Franklin x-ray head stand. This machine permits the proper positioning of the head for the clear visualization of the foramina at the base of the skull—particularly the foramen ovale, through which the needle is inserted, and its satellite foramen spinosum. The general details of approaching the gasserian ganglion through the foramen ovale have long ago been meticulously described by various investigators, (Härtel (5) 1912; Dorance (6) 1916; Harris (7, 8) 1912; Putnam and Hampton (9) 1936; Chouke (10) 1949; Penman (11) 1949) and should be first carefully studied by anyone undertaking this procedure. After piercing the skin with a sharp-pointed needle, a 17-gauge, 3-inch, thin-walled, spinal-puncture needle with a slightly dulled beveled point 4 millimeters in length is inserted through the skin of the cheek 3 centimeters below the malar bone and between the ramus of the mandible and the maxilla. It is thrust toward the well known anatomic location of the foramen ovale until it engages the base of the skull—using due caution to move the point about slightly so as not to pierce through the foramen ovale unknowingly. When the tip of the needle has been fixed in the periosteum, its exact location is visualized by a roentgenogram showing the base of the skull. The patient is positioned with the back of the head resting on a Potter-Bucky diaphragm film holder and the central ray of the tube passing below the lower jaw as nearly perpendicular to the base of the skull as possible (Fig. 1). Angling the tube slightly cephalad and lifting the mandible will facilitate clear visualization of the basal foramina. When the needle tip can be clearly seen in relation to the foramen ovale, it is moved the indicated distance in a direction so that it will enter this opening. At this point, the edges of the foramen can be palpated by the needle point and the sensation of entering the foramen is distinctly perceived. There is almost invariably a jerk of the lower jaw from compression of the motor root as it comes through the foramen. The precise location can be again verified by another roentgenogram (Fig. 2). From this point, the needle is advanced 12 millimeters

FIG. 1. Position of head on Franklin x-ray head-stand, for visualizing position of needle in relation to foramen ovale.

through the foramen and into the gasserian ganglion. The measurement must be approximated by estimating the distance the needle is advanced from the malar bone as the shaft is held firmly by the left hand. At some point between 12 and 17 millimeters from the foraminal edge, blood tinged cerebrospinal fluid may be obtained by jugular compression or syringe aspiration. This indicates that the needle tip has pierced the arachnoid reflexion surrounding the ganglion and sensory root of the fifth cranial nerve, and that it has been properly placed in the ganglionic subarachnoid fluid-bearing space (Meckel's cavity) for the injection. As the needle is advanced, its stylet is always kept in place, to prevent obstruction of the lumen from small blood clots. At the first sign of cerebrospinal fluid, 0.5 cc. of boiling distilled water is injected. With the patient under very light anesthesia, one can then demonstrate by pin prick an area of diminished sensation on the face corresponding to the well known anatomic distribution of the ganglion. If 2 cc. is injected into the fluid-bearing area of the ganglion at one time, the entire face will be almost completely anesthetized. It has been found necessary to repeat the injection with increasing amounts of boiling water, adding 0.5 cc. to each injection until the desired anesthesia is produced. As little as 0.5 cc. of boiling water may stop the pain without producing extensive sensory loss. However, it must be remembered that tic douloureux can, and often does extend into any area of the face where sensation remains following incomplete section of the sensory root or only partial destruction of the gasserian ganglion cells.



A B

FIG. 2. **a.** The needle can be seen at the foramen ovale and has been properly placed for deeper penetration. The satellite foramen spinosum is slightly posterior and lateral to the foramen ovale.

**b.** The needle has been advanced to the proper depth in the foramen ovale, at which point the injection should be started.

Under no circumstance should the needle be advanced beyond the petrous ridge, which is approximately 20 millimeters beyond the edge of the foramen ovale. If the foramen has been well entered and no fluid can be aspirated, it is advisable to inject the water repeatedly in small amounts until the desired sensory loss is obtained beyond that observed in the distribution of the third division. The hot water will seep backward into the ganglion cells and destroy them in proportion to the quantity of heat that reaches them. Therefore, the major sensory loss is usually due to cell destruction at the outer edge of the ganglion; by gradually increasing the amount, the second and third branches are affected as the heat reaches the mesial edge. Actually, good results were achieved in 12 of the 24 cases injected in this manner. The extent of the anesthetic or analgesic effect should not be gauged by the sensory loss produced over the area of the third division, since obviously branch destruction and not ganglion destruction may have caused the diminished sensation. In this instance, a regrowth of the nerve and return of the pain is certain.

Since this method is painless and produces no surgical shock, it can be repeated at once until the desired hypalgesic area is obtained. The anesthetic effect produced by destruction of ganglion cells has been permanent—which is a desirable result. Otherwise tic douloureux is incurable, except by a major intracranial surgical procedure or alcohol destruction of the ganglion. Actually, the temperature of the injected water has been measured at approximately 80° C. as it comes from the tip of the needle. As the water enters the cerebrospinal fluid, it is immediately cooled to an innocuous temperature by dilution and heat dispersion. It is improbable that any damage to the brain or other cranial nerves will result if less than 1 cc. of water is injected at any one time. This method has always

produced an immediate complete or partial paralysis of the muscles of mastication, which may be detected on careful examination of the masseter and temporal muscles. It is known that this is temporary and that the motor branch will regenerate in a few months.

### RESULTS OF HOT-WATER INJECTION (GASSERIAN GANGLION)

This follow-up study during the period September 4, 1953 to December 3, 1954, concerns 24 patients with intractable pain of the face, in whom the gasserian ganglion was injected with hot water. Included in this study are 18 cases of tic douloureux, 2 cases of atypical facial pain, and 4 cases of cancer of the face and jaws.

Of the 18 tic patients, all had some degree of anesthesia and hypalgesia following injection (Fig. 3), with the exception of 3 patients in whom there was total anesthesia of the entire side of the face and cornea. It is interesting that these 3 patients (thirteen, eight, and eight months later, respectively) had no discomfort or complications of any kind; the strength of the muscles of mastication was good, and lacrimation appeared normal. There were 3 failures in cases of tic douloureux in which the injection had been incomplete; these cases were later cured by suboccipital nerve-root section. One patient, in whom the injection was

A B

FIG. 3. **a.** Result, one year after hot-water injection limited to the second division of the gasserian ganglion. Pain disappeared, with minimal sensory loss. Lined areas represent anesthesia, and stippled areas represent hypalgesia.

**b.** Residual sensory loss eleven months following injection. Lined areas represent complete anesthesia; stippled areas represent hypalgesia. Pain was originally referable to the first and second divisions. Good result.

incomplete, refused root section or complete destruction of the ganglion, and continues to complain bitterly. Another had temporary relief, and practically no loss of sensation; a subsequent attempt failed, and relief was obtained by injection of the supraorbital nerve with alcohol. All 18 patients regained strength in the muscles of mastication, and although lacrimation was frequently diminished, it could be readily provoked by appropriate stimuli. There was not a single instance of facial paralysis or weakness. This is remarkable when one considers the significant incidence of this complication following subtemporal resection of the sensory root. Only 1 patient had herpes at the corner of the mouth and some immediate corneal and conjunctival congestion, both of which subsided in a few days. There was 1 mild case of transitory fourth cranial nerve paresis. Two patients had slight transitory impairment of hearing caused by accumulation of serum beneath the ear-drum following trauma of the eustachian tube. All these manifestations cleared up spontaneously in a period of several weeks.

The 2 patients with atypical facial pain were not helped. One of these subsequently underwent lobotomy and complete sensory-root section, without relief. Another had a mild meningeal reaction without complications.

The 4 patients with cancer of the face obtained satisfactory relief from pain following hot-water injection.

## SUMMARY

Experience with 18 patients suffering from tic douloureux, treated by injection of the gasserian ganglion with hot water (80°C.), indicates that it is a relatively safe procedure, if performed by a qualified surgeon. It was effective in 13 of the 18 patients, without a death or major complication.

As might be expected, the procedure gave no relief in 2 cases of atypical facial pain.

In 4 cases of facial cancer there was satisfactory relief of pain following injection.

Tic douloureux often affects people in their older years. The average age in our 18 patients was 64 years. It appears that the aged, as well as others, may be safely relieved of pain by the injection of hot water into the gasserian ganglion.

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# Abstracts of Current Literature

THE PROGNOSIS OF MAJOR SURGERY FOR CANCER IN THE AGED.

Anglem, T. J., and Bradford, M. L. *Cancer* **7:** 988 (Sept.) 1954.

A follow-up study of 258 patients having major surgical procedures for cancer showed that cure was possible in 168, or 65.1 per cent. Including operations for more than one independent cancer in the same patient and staged procedures, 174 curative operations for cancer were performed on patients with an average age of 75.2 years. The operative mortality was 11.5 per cent. Of these operations 115 were performed on 112 patients more than five years previously. For these cases there was a five-year-or-longer survival rate of 34.8 per cent. In 141 patients, the three-year survival rate was 39.7 per cent. In the two years prior to the report, despite the fact that somewhat older patients were accepted and surgical procedures of increasingly greater magnitude carried out, the operative mortality rate was reduced to 6.7 per cent. In the light of these results and the not inconsiderable life expectancy of patients even at these advanced ages, the authors believe that the benefits of surgery should not be denied the elderly cancer patient, on the basis of age alone.

PSEUDOINFLAMMATORY COLLOID CARCINOMA OF THE RECTUM.

Binkley, G. E., and Quan, S. H. Q. *Cancer* **7:** 1020 (Sept.) 1954.

Six case histories of pseudoinflammatory colloid carcinoma of the rectum are reported. This type of cancer is almost always overlooked and remains undiagnosed for long periods of time. Symptoms vary in early and moderately advanced stages. Early in the disease there may be no pain, but the feeling of a mass low in the rectum. Other complaints in the patients reported were painful defecation, narrowing of the caliber of the stool, and a sensation of swelling of the rectum. Pain was prominent in cases with secondary infection. The pseudoinflammatory process creates the impression of an abscess. Upon incision for drainage, no pus is found. The pseudoinflammatory or secondary infection, whichever is found on incision, usually induces a chronic fistula that discharges small amounts of purulent colloid, or gelatinous material. Systemic symptoms such as anorexia, weight loss, and weakness also occur in this kind of cancer as it advances toward its terminal stage. Rectal examinations show varying degrees of induration or tumor formation. Fistulas are commonly associated with the well-established disease. The greatest obstacle to diagnosis is the difficulty in obtaining cancer tissue by means of the ordinary type of biopsy. Cancer cells are few compared to the amount of induration, so that repeated biopsies, removal of large areas of induration or resection of the tumor are necessary to prove the presence of carcinoma. The histologic picture of this type of cancer is briefly stated. The disease has a slow rate of growth—3 cases ran courses of seven to ten years. Early recognition and surgical excision, including the removal of all contiguous organs invaded by direct extension, offer the best possibility of a satisfactory therapeutic result. Properly placed doses of radium in addition to irradiation with high-voltage roentgen rays have been valuable in producing comfort and extension of life.

OCCLUSIVE DISEASE OF THE AORTA AND ITS TREATMENT BY RESECTION AND HOMOGRAFT REPLACEMENT.

DeBakey, M. E., Creech, O., Jr., and Cooley, D. A. *Ann. Surg.* **140:** 290 (Sept.) 1954.

Observations were made on 22 patients with thrombo-obliterative disease of the aorta treated by resection of the aortic bifurcation and replacement with a lyophilized aortic homograft. Ten patients had a localized occlusive process, and 12 had partial aortic oc-

clusion. All the patients were white males, ranging in age from 33 to 63 years. Those with complete occlusion were almost a decade younger than those with incomplete occlusion. The clinical manifestations consisted essentially of slowly progressive symptoms of arterial insufficiency of the lower extremities, in addition to sexual impotence and hypertension in about one third of the cases. The average duration of symptoms for those with complete occlusion was four and a half years; and for the group with incomplete occlusion two and a half years. Aortography confirmed the clinical impression in the cases with complete aortic occlusion and established the presence and extent of the partial occlusive process. Aortic bifurcation homografts were implanted in all patients. In addition, homografts were placed in the iliac bifurcation in 4 cases, in the external iliac artery in 3 cases, in the common femoral artery in 2, and in the superficial femoral artery in 1 patient. On the basis of pathologic studies, the resected specimens were classified into two groups—those with complete, and those with partial occlusion. The gross and histologic appearances of the vessel wall and of the occluding thrombi suggest that the thrombo-obliterative process begins in the common iliac arteries and in the region of the aortic bifurcation, and involves more proximal segments by propagation. There were 2 deaths in the series. All but 4 of the remaining patients experienced striking improvement, with complete restoration of pulses in the lower extremities. On the basis of these observations it appears that the complete occlusive form of thrombo-obliterative disease is generally confined to the terminal aorta and bifurcation, and is ideally suited for resection with homograft replacement. On the other hand, the partially occluded process tends to be much less localized, and when associated with peripheral arteriosclerosis obliterans, the procedure of aortic resection and homograft replacement may be contraindicated. (Authors' summary.)

PRIMARY ADENOCARCINOMA OF THE RECTOVAGINAL SEPTUM PROBABLY ARISING FROM ENDOMETRIOSIS. REPORT OF TWO CASES.

Dockerty, M. B.; Pratt, J. H., and Decker, D. G. *Cancer* **7:** 893 (Sept.) 1954.

Two cases are presented wherein a malignant change occurred at the site of endometriosis of the rectovaginal septum. The literature on malignant transformation in pelvic endometriosis is reviewed briefly. In these patients repeated rectovaginal examinations failed to reveal the size and nature of the masses behind the cervix. Pelvic examinations helped to exclude the rectum, cervix, and vagina as the primary site of the tumor. It is recommended that in the patient past 40 years of age, no pelvic mass be assumed to be endometriosis until this diagnosis has been proved by surgical exploration and biopsy.

ZONE ELECTROPHORETIC STUDIES OF PLASMA PROTEINS IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS.

Hunt, T. E., and Trew, J. A. *Ann. Rheum. Dis.* **13:** 201 (Sept.) 1954.

A simple method of estimating the 5 major components of plasma protein is described and some of the problems and undesirable features of the technic discussed. By zone electrophoresis, in rheumatoid arthritis and ankylosing spondylitis, a moderate to marked rise is found in the relative fibrinogen and gamma-globulin levels, while the plasma albumin tends to be correspondingly reduced. No significant alterations in alpha- and beta-globulins are apparent. Studies relating sedimentation rates to plasma fibrinogen levels in rheumatoid disease again demonstrate a linear correlation between them. The correlation is not as impressive with fibrinogen percentage levels obtained by zone electrophoresis as with the estimations obtained by precipitation with sodium sulphite. The former correlation is, however, statistically significant and indicates that the technic is suitable for general clinical use, particularly in patients with rheumatoid disease. The progress of several patients was followed during cortisone, phenylbutazone, and gold therapy and graphs are presented utilizing the sedimentation rate and plasma fibrinogen level determined by zone electrophoresis as indices of the activity of rheumatoid disease.

EVALUATION AND PREPARATION OF THE POOR-RISK PATIENT WITH CANCER FOR MAJOR SURGERY.

La Due, J. S., and Wroblewski, F. *Cancer* **7:** 797 (Sept.) 1954.

Operative risk can be evaluated only when detailed clinical and laboratory data are available. Methods for obtaining this information are outlined. The poor-risk patient is defined from the point of view of nutritional, endocrine, hepatic, renal, respiratory, and cardiovascular disease. Age is usually considered to constitute an operative risk but results of 188 major operations for cancer in 161 patients 70 years of age or older indicate that elderly persons survive surprisingly well. Contraindications to major surgery for cancer are delineated. Measures are outlined whereby some patients may be removed from this category and other types of poor-risk patients prepared for major surgical operations.

MALIGNANT SYNOVIOMA SIMULATING "ADAMANTINOMA OF THE TIBIA."

Lederer, H., and Sinclair, A. J. *J. Path. & Bact.* **67:** 163 (July) 1954.

A case of malignant synovioma invading the tibia is described, the histologic and clinical features of which resemble those attributed to so-called adamantinoma of the tibia. The literature on tibial adamantinoma is reviewed and a recommendation made that recognition of "adamantinoma" of the tibia as a separate entity be discontinued. It is thought that most, if not all of the tumors reported as tibial adamantinomas may have been synoviomas. The descriptions and photomicrographs of tumors described as the former are interchangeable with those of malignant synovioma. The clinical attributes are similar—slow growth a tendency to recur after local excision, predilection for the lower extremity, and insensitivity to irradiation.

PROPHYLAXIE DES RAIDEURS, OEDÈMES, RARÉFACTIONS OSSEUSES QUI PERSISTENT APRÈS CONSOLIDATION DES FRACTURES SPÉCIALEMENT CHEZ LES GENS AGÉS. (PROPHYLAXIS OF STIFFNESS, EDEMA, AND OSSEOUS RAREFACTION WHICH PERSIST AFTER CONSOLIDATION OF FRACTURES ESPECIALLY IN ELDERLY INDIVIDUALS).

Leriche, R. *Presse méd.* **62:** 1223 (Sept. 18) 1954.

The author attributes edema and stiffness following fractures to post-traumatic vasomotor disturbances. To avoid these sequelae, he recommends repeated local infiltration of the focus of the fracture, sympathetic blockade, and intra-arterial injection of procaine, which together correct the post-traumatic vasomotor derangements.

THE DIAGNOSIS OF CARCINOMA OF THE PANCREAS.

Leveaux, V. M. *Brit. J. Cancer* **8:** 427 (Sept.) 1954.

The historical background of carcinoma of the pancreas is briefly reviewed. A series of 46 cases proven at operation is considered from the clinical, radiologic and biochemical aspects, in an attempt to clarify the helpful diagnostic features. The high incidence and the importance of pain and weight loss as symptoms are emphasized. Jaundice is found to occur less frequently than either of the symptoms mentioned, and to be painless in relatively few cases. A relationship between the anatomic position of the tumor and the site of the pain complained of by the patient is suggested. A scheme of investigation is proposed which includes careful radiologic studies, a glucose tolerance test, serum lipase and amylase determinations and a Bromsulphalein retention test. Surgical exploration is advocated when strong clinical grounds alone exist.

SODIUM SALICYLATE AND PROBENECID IN THE TREATMENT OF CHRONIC GOUT. ASSESSMENT OF THEIR RELATIVE EFFECTS IN LOWERING SERUM URIC ACID LEVELS.

Marson, F. G. W. *Ann. Rheum. Dis.* **13:** 233 (Sept.) 1954.

The effects of salicylate and probenecid in lowering the serum uric acid level of gouty patients were compared. A maximum fall in the serum uric acid level occurs within a few days of commencing salicylate or probenecid. This is not maintained and gives an exaggerated impression of the effects of either drug during prolonged therapy. Seventeen chronic gouty patients received continuous salicylate therapy for from nine to forty-five months. The mean level of serum uric acid was 50 per cent of the initial level, and in 13 of the 17 patients the uric acid concentration was maintained below the normal mean level in healthy subjects. Six chronic gouty patients received probenecid for from twelve to nineteen months. The mean level of serum uric acid was 68 per cent of the initial level, and in 1 of the 6 patients the uric acid concentration was maintained at lower than the normal mean level. Four patients received salicylate and probenecid at different periods. In each case salicylate had a greater depressant effect on the serum uric acid level. Single doses of 100 grains (6.5 Gm.) of sodium salicylate had approximately double the uricosuric effect of single doses of 2 Gm. of probenecid during the six hours following administration of the drugs. The coincident administration of probenecid and salicylates did not nullify the uricosuric effect. Toxic symptoms occurred in 9 of the 15 patients receiving probenecid. A rapid tolerance usually developed, but 2 severe reactions (headache, unconsciousness, maculopapular rash) were encountered which necessitated withdrawal of the drug.

EXPERIENCES WITH THE MANAGEMENT OF SEVERE BLEEDING FROM PEPTIC ULCER.

Mayo, H. W., Jr., and Owens, J. K. *Surgery* **36:** 412 (Sept.) 1954.

A series of 99 cases of bleeding from peptic ulcer is presented. Of these, 47 patients were classified as having severe hemorrhage. There was 1 death in 76 cases treated conservatively, and 4 deaths in 23 patients treated by operative measures. One other patient failed to survive elective surgery performed after cessation of the bleeding. A method of combined medical and surgical therapy is presented, emphasis being placed on the importance of giving adequate blood transfusions in the treatment of bleeding ulcer, individualization of cases in choosing those which require emergency gastric resection, and the serious prognostic significance of 1) gastric ulcer associated with severe hemorrhage, and 2) poor initial response to transfusions or recurrence of bleeding after the institution of medical therapy. In patients with severe hemorrhage from gastric ulcer, in those who show a poor or unsustained response to adequate transfusions early in the course of management, and in those who bleed again after cessation of hemorrhage, there is a poor prognosis, and these patients should be selected for emergency gastric resection. When esophageal varices have been uled out, and it has been determined that the hemorrhage is arising from the stomach or duodenum, even if an ulcer cannot be demonstrated at laparotomy, empiric gastric resection should be performed.

POSTOPERATIVE MORTALITY AFTER TOTAL GASTRECTOMY.

McNeer, G., and Pack, G. T. *Cancer* **7:** 1010 (Sept.) 1954.

The operative mortality for simple total gastrectomy at Memorial Center (New York) was reduced from a high of 30 per cent to 11.4 per cent in a series of 35 operations. Radical total gastrectomy, however, resulted in an operative mortality rate of 26.3 per cent. In 52 per cent of the fatal cases, the patients died of anastomotic leaks and peritonitis, although there was no change in the number or type of anastomoses in the period when an increased rate occurred, as opposed to an earlier period. The reasons for the increased operative

mortality after extended radical total gastrectomy were therefore sought, and the following conclusions drawn: An increased resectability rate from 21.6 per cent (1931 through 1942) to 64.6 per cent (1948 through 1952) showed greater surgical aggressiveness. More gastric cancers were rendered resectable by laparothoracotomy. The wounds in this operation required additional time to open and to close. Older patients did not tolerate extended total gastrectomy as well as did younger individuals. The selection of operative technic in older poor-risk patients should possibly be more careful. Simple esophagojejunostomy appears to be the method of choice for restoring esophagojejunal continuity, as it requires only one anastomosis and carried the lowest operative mortality. Deaths are due to technical and correctable failures in many instances. A higher operative mortality rate in ward patients as compared with private patients suggests the need for more closely integrated effort by the staff assigned to these patients.

PERITONEAL MESOTHELIOMA. CASE REPORT.

Pendergrass, E. P., and Edeiken, J. *Cancer* **7:** 899 (Sept.) 1954.

A case of peritoneal mesothelioma was treated by irradiation with a total of 9,650 tissue roentgens over a four-year period. The patient's health remained relatively good during treatment. Thereafter, the tumor became refractory and the patient died. The tumor was reduced in size by 2,500 tissue roentgens but reactivation of growth took place within a few months. Relief of pain was also obtained by radiation. A review of cases of peritoneal mesothelioma in the literature shows that males are more often affected than females. The age group has extended from 32 to 71 years. There may be no symptoms referable to the lesion in the early stages, or there may be vague abdominal pain. As the disease progresses, ascitic fluid tends to appear, and nausea, vomiting, and abdominal discomfort may result. Other symptoms may be weight loss, change in bowel habits, or a tender nodule. The course may be rapidly fatal after fluid appears, but in its absence the general health may not be affected for long periods. The lesions, which usually are small and are characteristically grayish, spread over all parts of the peritoneum but may be most numerous on the mesentery. The tumor spreads by direct extension to the thorax and viscera, but solitary metastases deep in the liver parenchyma have been reported. Of the cases reviewed none was treated by radiation.

APOCRINE-GLAND ADENOCARCINOMA AND EXTRAMAMMARY PAGET'S DISEASE OF THE VULVA. REVIEW OF THE LITERATURE AND REPORT OF A CASE.

Plachta, A., and Speer, F. D. *Cancer* **7:** 910 (Sept.) 1954.

A case of extramammary Paget's disease of the vulva originating in an apocrine-gland adenocarcinoma is presented, including its prolonged clinical aspects and its complete necropsy findings. The more important contributions in the literature on extramammary Paget's disease are briefly reviewed, and the numerous uncertainties in the diagnosis and in the nature and histogenesis of the condition are emphasized. The importance of this report is in relation to the serial sections of the vulva and their detailed study with microphotographs that clearly show a mucogenic apocrinegland adenocarcinoma with Paget's cells in the ducts of these glands and in the overlying epidermis. Such findings prove as much as any microscopic study can, that epidermal extrammary Paget's disease is related to apocrine-gland adenocarcinoma. Thus the detailed analogy between Paget's disease of the breast nipple, as suggested by Cheatle and Cutler, and extramammary Paget's disease, as suggested by Weiner, is established. It is important to emphasize that this lesion may be difficult to diagnose without large, and possibly multiple biopsy specimens; that its evolution is prolonged; but that it is a very dangerous lesion, since generalized metastases seem to be the rule. Unfortunately this case report offers no solution to the problem of extramammary Paget's disease unassociated with epidermal adnexal carcinoma. Whether such lesions exist and whether they should be referred to as extramammary Paget's disease must be left for future studies.

ATYPICAL NEURALGIA OF THE CHEST SIMULATING ANGINA PECTORIS.

Reichert, F. L. *Am. J. Surg.* **88:** 399 (Sept.) 1954.

Atypical neuralgia or post-traumatic pain syndrome involving the chest and resembling angina pectoris is unusual and occurs less frequently than true angina pectoris. The principal sources of irritation in the chest are sprains or strains of the origins of the pectoral muscles, and at times of the trapezius, deltoid, and supraspinatus muscles. The prolonged anxiety of a patient under a mistaken diagnosis of angina pectoris, whose activity is restricted because of fear of a coronary thrombosis, and because of exhaustion from pain, may precipitate and perpetuate an alarm reaction that progresses in severity. Patients so affected have subclinical and clinical signs of vitamin and endocrine insufficiency, age perceptibly, and often show marked personality changes. It is always possible that remote disease of the viscera may give rise reflexly to trigger areas in the musculofascular regions. In the 30 cases of atypical neuralgia presented, visceral disease was repeatedly proved absent. Treatment consists of injecting the trigger points with 2 per cent procaine hydrochloride. Its success depends upon accurate identification and painstaking infiltration of sensitized areas. All patients should receive a barbiturate prior to the injection of procaine, as its toxicity is thus reduced fivefold. Pain down the arm can be relieved by procaine injections into the potential bursa between the spinous process of the lower cervical and upper thoracic vertebrae.

THE USE OF PLIABLE PLASTIC TUBES AS AORTIC SUBSTITUTES IN MAN.

Schumacker, H. B., and King, H. *Surg., Gynec. & Obst.* **99:** 287 (Sept.) 1954.

This is the first report of the use of pliable plastic tubes as vascular substitutes in man. The material for tubes was made by fusing a thin sheet of nonreactive polythene between two sheets of nylon and then stitching tubes of desired sizes and shapes on a sewing machine. The material can be autoclaved and is impervious to blood. The same objective can be achieved by coating nylon with methyl methacrylate but the polythene tubes are believed to be superior. In 10 patients with aneurysms, grafts of the aorta or the aortic bifurcation functioned well. Nine were made with nylon and polythene and 1 with methyl methacrylate. These results and those of experimental studies are felt to justify the expansion of clinical observations on the use of the pliable plastic tubes.

PORTAL-SYSTEMIC ENCEPHALOPATHY. NEUROLOGICAL COMPLICATIONS OF LIVER DISEASE.

Sherlock, S.; Summerskill, W. H. J.; White, L. P., and Phear, E. A. *Lancet* **2:** 453 (Sept. 4) 1954.

The neurologic complications observed in 18 patients with liver disease are described, and their relation to hepatocellular disease, portal collateral circulation, and exciting agents is demonstrated. A syndrome associated with thrombotic occlusion of the portal vein in patients with cirrhosis of the liver, or arising as a sequel to portal-systemic shunt operations, is described. Evidence is advanced that nitrogenous substances of portal venous origin, normally metabolized in the liver, may reach the systemic circulation through a damaged liver, through portal collateral channels, or through both, and cause a cerebral disturbance (portal-systemic encephalopathy). The nature of the metabolic disorder is considered, with particular reference to deranged ammonia metabolism. Principles of treatment are discussed. These include the withdrawal of any specific identifiable exciting agent. (The exciting agents in the patients examined were: high-protein diet, ammonium chloride, methonine, gastrointestinal hemorrhage, paracentesis or operation, infection, and extreme liver failure.) Nitrogen intake should be reduced to a minimum and caloric requirements supplied by means of glucose administered by the simplest route. Chemotherapy may be used to reduce bacterial action in the intestines. Following an enema, daily evacuation should be ensured by an effective purge.

THE INFLUENCE OF THE THYROID IN MALIGNANT DISEASE.

Spencer, J. G. C. *Brit. J. Cancer* **8:** 393 (Sept.) 1954.

Data from 15 countries in four continents give support to the importance of local factors in accounting for the known local variations of cancer incidence. Iodine availability, traced by the incidence of goiter, appears to be one of such factors. Closer scrutiny of some of the countries corroborates these conclusions. Clinical findings and a review of some of the experimental work available lend further emphasis to these observations. The apparent relationship of thyroid insufficiency and the liability to develop cancer is discussed in connection with such other hormonal influences over cancer as are already known, particularly in respect of the pituitary. Lines of investigation and clinical trials have been started, but results of any value cannot be expected for several years. A nonspecific organ immunity or susceptibility seems to be the simplest explanation of the facts presented, and the possibilities, preventive and perhaps therapeutic, that are opened up by this line of research are briefly discussed.

EXTRAPROSTATIC FACTORS IN URINARY RETENTION.

Talbot, H. S. *New England J. Med.* **251:** 420 (Sept.) 1954.

Patients with prostatic enlargement and other types of obstruction at the bladder neck may have concomitant disturbances that contribute significantly to the micturitional dysfunction. One of these is pre-existing stricture of the distal urethra. Decompensation of the detrusor may exist coincidentally with the obstruction, although etiologically independent of it. This may be a result of a structural or a purely functional deficiency, or both. This type of dysfunction may be corrected, in some cases, by the elimination of the associated obstruction. A more important type of dysfunction results from the alterations in the wall of the bladder that develop in consequence of long-standing obstruction. These may be reversible to the degree that they do not prevent the resumption of normal function after operative removal of the obstructing factor. A satisfactory result, however, may require careful conservative management after operation, with particular attention to habit training. These alterations are sometimes irreversible in the sense that, after removal of the obstruction, satisfactory function is not restored by any methods short of further surgical intervention. This usually takes the form of a partial cystectomy, the redundant portion of the bladder wall being removed. In every patient presenting a disorder of micturition, even when an obstruction is obvious, careful evaluation should be made of all the factors involved in micturitional function. This will be of aid in the charting of a suitable course of preoperative and postoperative treatment. The investigations involved—cystometry, cystography and frequent checking of the residual urine—are simple, safe and inexpensive. (Author's conclusions.)

A CLINICAL STUDY OF THE EFFECTS OF INTRAVENOUS RESERPINE (SERPASIL) IN HYPERTENSIVE PATIENTS.

Tuchman, H.; Sletten, I. W., and Crumpton, C. W. *Am. Heart J.* **48:** 449 (Sept.) 1954.

The effect of a single intravenous injection of 0.5 or 1.0 mg. of reserpine was studied in 23 hospital patients aged 40 to 64 years, with moderate to severe hypertension. In 13 there was a fall in blood pressure to normotensive levels and/or a reduction in the calculated mean average blood pressure of 20 mm. of Hg or more. Nineteen patients had mild side effects—nasal stuffiness, facial flush, and lethargy. A sodium Amytal test was performed in 15 of the 23 patients and the blood pressure response compared with the effect of intravenous reserpine. In general, patients in whom the mean average blood pressure fell 20 mm. of Hg or more with sodium Amytal showed a comparable blood pressure reduction following intravenous reserpine. On the basis of these observations it is hypothesized that

patients who show significant blood pressure reduction with sodium Amytal may also respond to the alkaloids of *Rauwolfia serpentina*. The comparable degrees of blood pressure reduction suggest that the ability of Rauwolfia compounds to reduce blood pressure may be related to a sedative effect rather than to a specific effect upon the cardiovascular system.

BURIED METALLIC PROSTHESIS FOR MANDIBULAR DEFECTS.

Walsh, T. S. *Cancer* **7:** 1002 (Sept.) 1954.

The successful use of a buried metallic prosthesis for mandibular defects following excision of cancer of the floor of the mouth in 8 cases is described. The operative procedure and that for inserting the metallic bar are outlined. The criterion of success has been that the metal remained in place for a minimal period of five months in all cases. Tumor usually recurs within this arbitrary time limit. Soft tissues have been maintained in position without contractures. Permanent reconstructive steps are deferred until the chances of recurrence are remote.

TREATMENT OF PARKINSONISM WITH PAGITANE HYDROCHLORIDE. RESULTS IN 142 PATIENTS.

Zier, A., and Doshay, L. J. *Neurology* **4:** 682 (Sept.) 1954.

A new synthetic drug, Pagitane hydrochloride, has already been reported in the literature. The present report is a clinical survey of its action in a series of 142 patients with parkinsonism, who had had poor results with other remedies. Of this number, 94 (66 per cent) manifested improvement of varying degree, 40 (28 per cent) were unimproved, and 8 (6 per cent) appeared to be worse. The study covered a period of fifteen months. Methods of administration and procedure are described. Pagitane hydrochloride was found to be considerably more potent than Artane and less disturbing in its side reactions, especially dryness of the mouth and mental clouding. It is possible that within several years, as in the case of Artane, it may be found that the effects wear off in a larger percentage of patients than is evident now, or patients may tire of it and turn to some new preparation. Nevertheless, the fact that so many of them have chosen to continue taking it establishes the drug as a valuable addition to the armamentarium for the treatment of parkinsonism. Pagitane can be administered to all types of cases. Other than the usual side reactions of belladonna products and their congeners, no toxic effects were noted among the patients in this study. It is safe for both young and old patients, and may be employed as the drug of choice in starting the treatment of new cases. It exerts a favorable action against rigidity, oculogyria, and mild forms of tremor. It is a powerful cerebral stimulant and serves to counteract akinesia, sluggishness, tiredness, and weakness. For more effective action against advanced stages of rigidity and tremor, it readily combines with other drugs, such as hyoscine, Benadryl, atropine, or Cogentin. It is especially beneficial as a substitute for Artane among patients in whom the latter drug no longer controls symptoms.

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